RECEIVED
JAN 29 2002

Access DB# 59227

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: STIC Geetha Bansal Examiner #: 73967 Date: 1/28/02
Art Unit: 1642 Phone Number 305-3955 Serial Number: 09/522900
Mail Box and Bldg/Room Location: CM1-8A03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MEJ

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Self Antigen Vaccines for Treating B cell lymphoma

Inventors (please provide full names): McCormick, Alison; TUSE, Daniel; Reinl, Stephen; LINDBO; TURPEN, Thomas

Earliest Priority Filing Date: Sept 24, 1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Point of Contact:
Beverly Shears
Technical Info. Specialist
CM1 ~~1201~~4 Tel: 308-4994
1E05

Please Search;

1. Plant Produced Antigen or Vaccine for B cell lymphoma

2. Anti-idiotype vaccine for B cell lymphoma produced in a plant system

3. Above vaccine comprises at least 1 CDR from V_H or includes CDR_2.

4. Plant produced single chain F_v (scFv) ~~for B cell~~ or antibody fragment

5. Above as in 4, wherein the linker molecule between 2 domains is 1-50 residues and promotes correct folding of the polypeptide

****

STAFF USE ONLY

Searcher: Beverly C 4994
Searcher Phone #:
Searcher Location:
Date Searcher Picked Up:
Date Completed: 02-05-02
Searcher Prep & Review Time: 12
Clerical Prep Time:
Online Time: 21

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

STN ✓
Dialog
Questel/Orbit
Dr.Link
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (1-2000)

(FILE 'CAPLUS' ENTERED AT 12:06:42 ON 04 FEB 2002)
L1 3353 S B(1W)LYMPHOMA
L2 13 S L1 AND PLANT

L2 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:697651 CAPLUS
TITLE: Enzymic nucleic acids for the modulation and diagnosis of human CD20 and NOGO gene expression
INVENTOR(S): Blatt, Lawrence; McSwiggen, James; Chowrira, Bharat M.
PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 200 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001059103	A2	20010816	WO 2001-US4273	20010209

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2000-181797 P 20000211
US 2000-185516 P 20000228
US 2000-187128 P 20000306

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, and antisense oligonucleotides, which modulate the expression of the human CD20 and/or NOGO genes. The known sequences of human CD20 and NOGO mRNAs are screened for accessible sites using a computer-folding algorithm for regions that do not form secondary folding structures and thus may act as binding/cleaving sites. Thousands of target site and enzymic nucleic acid sequences are provided (hammerhead, Inozymes G-cleaver, Zinzymes Amberzymes, and DNAzymes). Several oncol. models in rodent, rabbit, and non-human primates are utilized to evaluate the therapeutic potential of anti-CD20 enzymic nucleic acids. Diagnostic systems and methods for detecting the presence of nucleic acids are further disclosed, using a ribozyme effector mol. and nucleic acid inhibitors complementary to the ribozyme and nucleic acid-based reporter mols. [This abstr. record is the second of two records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L2 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:693353 CAPLUS
DOCUMENT NUMBER: 135:271876

TITLE: Self antigen vaccines for treating **B** cell **lymphomas** and other cancers
INVENTOR(S): Reinl, Stephen J.; Turpen, Thomas H.
PATENT ASSIGNEE(S): Large Scale Biology Corporation, USA; McCormick, Alison A.; Tuse, Daniel
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068682	A1	20010920	WO 2000-US28362	20001013

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-522900 A 20000310

AB A polypeptide self-antigen useful in a tumor-specific vaccine mimics one or more epitopes of an antigen uniquely expressed by cells of the tumor. The polypeptide is preferably produced in a **plant** that has been transformed or transfected with nucleic acid encoding the polypeptide and is obtainable from the **plant** in correctly folded, preferably sol. form without a need for denaturation and renaturation. This **plant** -produced polypeptide is immunogenic without a need for exogenous adjuvants or other immunostimulatory materials. The polypeptide is preferably an scFv mol. that bears the idiotype of the surface Ig of a non-Hodgkin's (or **B** cell) **lymphoma**. Upon administration to a subject with lymphoma, the **plant** -produced, tumor-unique scFv polypeptide induces an idiotype-specific antibody or cell-mediated immune response against the lymphoma.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:598168 CAPLUS
DOCUMENT NUMBER: 135:192168
TITLE: Enzymic nucleic acids for the modulation and diagnosis of human CD20 and NOGO gene expression
INVENTOR(S): Blatt, Lawrence; Mcswiggen, James; Chowrira, Bharat M.
PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 200 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001059103 A2		20010816	WO 2001-US4273	20010209

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR

PRIORITY APPLN. INFO.: US 2000-PV181797 20000211
US 2000-PV185516 20000228
US 2000-PV187128 20000306

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, and antisense oligonucleotides, which modulate the expression of the human CD20 and/or NOGO genes. The known sequences of human CD20 and NOGO mRNAs are screened for accessible sites using a computer-folding algorithm for regions that do not form secondary folding structures and thus may act as binding/cleaving sites. Thousands of target site and enzymic nucleic acid sequences are provided (hammerhead, Inozymes G-cleaver, Zinzymes Amberzymes, and DNAzymes). Several oncol. models in rodent, rabbit, and non-human primates are utilized to evaluate the therapeutic potential of anti-CD20 enzymic nucleic acids. Diagnostic systems and methods for detecting the presence of nucleic acids are further disclosed, using a ribozyme effector mol. and nucleic acid inhibitors complementary to the ribozyme and nucleic acid-based reporter mols. [This abstr. record is the first of two records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L2 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	2000:783469 CAPLUS
DOCUMENT NUMBER:	134:69519
TITLE:	Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma
AUTHOR(S):	Uren, Anthony G.; O'Rourke, Karen; Aravind, L.; Pisabarro, M. Teresa; Seshagiri, Somasekar; Koonin, Eugene V.; Dixi, Vishva M.
CORPORATE SOURCE:	Genentech Inc., South San Francisco, CA, 94080, USA
SOURCE:	Mol. Cell (2000), 6(4), 961-967
	CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER:	Cell Press
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Caspases are cysteine proteases essential to apoptosis. The authors have identified two families of caspase-like proteins, Paracaspases (found in metazoans and Dictyostelium) and metacaspases (found in **plants**, fungi, and protozoa). Metazoan paracaspase prodomains contain a death domain and Ig domains. Several **plant** metacaspase prodomains contain zinc finger motifs resembling those in the **plant** hypersensitive response/cell

death protein Isd-1. The human paracaspase prodomain binds Bcl10, a protein involved in the t(1;14)(p22;q32) translocation of mucosa-assocd. lymphoid tissue (MALT) lymphoma. Another MALT lymphoma translocation, t(11;18)(q21;q21), fuses the IAP-2 gene to the MLT1/MALT1 locus, which encodes the human paracaspase. The authors find that this fusion activates NF-.kappa.B and that the caspase domain is required for this function, since mutation of the conserved catalytic cysteine attenuates NF-.kappa.B activation.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:63485 CAPLUS
DOCUMENT NUMBER: 130:250885
TITLE: Rapid production of specific vaccines for lymphoma by expression of the tumor-derived single-chain Fv epitopes in tobacco plants
AUTHOR(S): McCormick, Alison A.; Kumagai, Monto H.; Hanley, Kathleen; Turpen, Thomas H.; Hakim, Itzhak; Grill, Laurence K.; Tuse, Daniel; Levy, Shoshana; Levy, Ronald
CORPORATE SOURCE: Biosource Technologies, Inc., Vacaville, CA, 95688, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1999), 96(2), 703-708 19 Jan 99
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rapid prodn. of protein-based tumor-specific vaccines for the treatment of malignancies is possible with the **plant**-based transient expression system described here. The authors created a modified tobamoviral vector that encodes the idiotype-specific single-chain Fv fragment (scFv) of the Ig from the 38C13 mouse B cell lymphoma. Infected Nicotiana benthamiana **plants** contain high levels of secreted scFv protein in the extracellular compartment. This material reacts with an anti-idiotype antibody by Western blotting, ELISA, and affinity chromatog., suggesting that the **plant**-produced 38C13 scFv protein is properly folded in soln. Mice vaccinated with the affinity-purified 38C13 scFv generate >10 .mu.g/mL anti-idiotype Igs. These mice were protected from challenge by a LD of the syngeneic 38C13 tumor, similar to mice immunized with the native 38C13 IgM-keyhole limpet hemocyanin conjugate vaccine. This rapid prodn. system for generating tumor-specific protein vaccines may provide a viable strategy for the treatment of non-Hodgkin's lymphoma.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:771830 CAPLUS
DOCUMENT NUMBER: 128:59423
TITLE: Water permeability of plasma membranes of cultured rice, grape, and CH27 cells measured

dielectrically
AUTHOR(S): Ishikawa, Eisuke; Miyawaki, Osato; Nakamura, Kozo
CORPORATE SOURCE: Department of Applied Biological Chemistry, The University of Tokyo, Tokyo, 113, Japan
SOURCE: Biosci., Biotechnol., Biochem. (1997), 61(11), 1826-1830
CODEN: BBBIEJ; ISSN: 0916-8451
PUBLISHER: Japan Society for Bioscience, Biotechnology, and Agrochemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The capacitance of suspensions of cultured rice cells (Oryza sativa L. ssp. japonica), grape cells (Vitis sp.), and CH27 cells originated from murine **B**-cell **lymphoma** was measured in the frequency range of 0.2 to 10 MHz. The relationship between the increase in capacitance caused by the presence of cells at 0.4 MHz, .DELTA.C, and the cell d. was linear. Measurement of capacitance was useful in measurement of transitional changes in cell vol. under external osmotic stress when sucrose was added. From the course of vol. changes with such stress, the water permeabilities of the plasma membrane, Lp, were measured to be 0.015, 0.020, and 0.090 pm/(s.cntdot.Pa) at 25.degree., for rice cells, grape cells, and CH27 cells, resp. The smaller Lp for **plant** cells seemed to explain why preservation of **plant** cells by freezing is more difficult than for animal cells. From the temp. dependence of Lp, the apparent activation energies were calcd. to be 12.0.+-.2.9 and 13.0.+-.5.2 kcal/mol for rice cells and CH27 cells, resp.

L2 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:501465 CAPLUS
DOCUMENT NUMBER: 127:120706
TITLE: Jun kinase and p38 MAP kinase regulation via CD40 signaling
INVENTOR(S): Gelfand, Erwin W.; Johnson, Gary L.
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9722256	A1	19970626	WO 1996-US20731	19961219
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6132978	A	20001017	US 1996-769747	19961219
US 2001055753	A1	20011227	US 2001-794258	20010227

PRIORITY APPLN. INFO.: US 1995-8877 P 19951219
US 1996-769747 A3 19961219
US 1999-361436 B1 19990726

AB The present invention discloses methods useful for identifying compds. capable of specifically controlling CD40 regulation of Jun

N-terminal kinase or p38 MAP kinase activity. In this method, CD40-expressing cells, following a stimulatory step, are assessed for responses to regulatory compds. whose effects are observable by way of their interference with kinase activation. Application of these compds. to inhibiting Ig heavy chain class switching, cytokine prodn. and activation of cells involved in an inflammatory response is described. The present invention also includes kits to perform such assays and methods to control disease related to such responses.

L2 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:326866 CAPLUS
DOCUMENT NUMBER: 126:308798
TITLE: Chimeric DNA-binding/DNA methyltransferase nucleic acid and polypeptide and their uses
INVENTOR(S): Bestor, Timothy H.
PATENT ASSIGNEE(S): Trustees of Columbia University in the City of New York, USA; Bestor, Timothy H.
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9711972	A1	19970403	WO 1996-US15576	19960927
W: AU, CA, JP, MX, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9673781	A1	19970417	AU 1996-73781	19960927

PRIORITY APPLN. INFO.: US 1995-4445 19950928
US 1996-594866 19960131
WO 1996-US15576 19960927

AB The present invention provides a chimeric protein which comprises a mutated DNA methyltransferase portion and a DNA binding protein portion that binds sufficiently close to a promoter sequence of a target gene (which promoter sequence contains a methylation site) to specifically methylate the site and inhibit activity of the promoter and thus inhibit expression of the target gene. This invention also provides for a method for inhibiting the expression of a target gene which includes contacting a promoter of the target gene with the chimeric protein, so as to specifically methylate the promoter sequence of the target gene thus inhibiting expression of the target gene.

L2 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:391732 CAPLUS
DOCUMENT NUMBER: 125:50731
TITLE: Multifunctional molecular complexes for gene transfer to cells
INVENTOR(S): Boutin, Raymond H.
PATENT ASSIGNEE(S): Apollon, Inc., USA
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9610038	A1	19960404	WO 1995-US12502	19950928
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5837533	A	19981117	US 1994-314060	19940928
CA 2201396	AA	19960404	CA 1995-2201396	19950928
AU 9537317	A1	19960419	AU 1995-37317	19950928
AU 704796	B2	19990506		
EP 789708	A1	19970820	EP 1995-935213	19950928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10506901	T2	19980707	JP 1995-512052	19950928
US 6127170	A	20001003	US 1997-809397	19970321

PRIORITY APPLN. INFO.: US 1994-314060 A 19940928
WO 1995-US12502 W 19950928

OTHER SOURCE(S): MARPAT 125:50731

AB A multifunctional mol. complex for the transfer of a nucleic acid compn. to a target cell is provided. The complex is comprised of A) said nucleic acid compn. and B) a transfer moiety comprising 1) one or more cationic polyamines bound to said nucleic acid compn., 2) one or more endosome membrane-disrupting components attached to at least one nitrogen of the polyamine and 3) one or more receptor-specific binding components. The receptor-specific binding component may be attached to the polyamine/membrane-disrupting component conjugate or it may be attached to another polyamine. These compns. may be used for transformation of microbes and **plant** and animal cells, for immunization, and for disease treatment. N4-(5-[N2,N4-bis(.beta.-3'-propionylgalactosyl-.beta.1,4-thioglucoside)lysyl-N6-(.beta.-3'-propionylgalactosyl-.beta.-1,4-thioglucoside)lysyl]aminopentyl)spermidine and N4-(5-cholestene-3'-.beta.-oxycarbonyl)aminopentyl)spermidine were synthesized. A soln. contg. these two compds. and a plasmid were employed to transform human hepatocellular carcinoma HuH7 cells.

L2 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:225437 CAPLUS
DOCUMENT NUMBER: 124:331285
TITLE: Targeted therapy of cancer and autoimmune diseases
AUTHOR(S): Press, Oliver W.; Wijdenes, John; Glennie, Martin J.; Bagshawe, Kenneth D.
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, University Washington, Seattle, USA
SOURCE: Pharmacol. Sci.: Perspect. Res. Ther. Late 1990s, [Int. Congr. Pharmacol.], 12th (1995), Meeting Date 1994, 381-9. Editor(s): Cuello, A. Claudio; Collier, Brian. Birkhaeuser: Basel, Switz.
CODEN: 62PPA6

DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 13 refs. Antibody-conjugates represent a promising new modality for refractory malignancies and autoimmune diseases that may afford greater selectivity and lesser toxicity than conventional cytotoxic treatments. Many types of immunoconjugates have been described including antibodies conjugated to conventional chemotherapeutic agents, **plant** toxins, bacterial toxins, radionuclides, and enzymes. We describe four promising new approaches. First, clin. trials employing unconjugated monoclonal antibodies targeting CD4 or the IL2 receptor are described for patients with autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and acute graft vs. host disease. Second, preclin. and clin. trials employing bispecific monoclonal antibodies recruiting the toxin, saporin, to idiotypic Igs or the CD22 antigen on **B**-cell **lymphomas** are discussed. Third, the use of antibody-enzyme conjugates in conjunction with prodrug substrates is presented. Finally, the use of radiolabeled anti-CD20 antibodies for treating patients with refractory **B**-cell **lymphomas** is summarized. Each of these methods has demonstrated impressive therapeutic results in preclin. models and clin. trials, warranting further investigation.

L2 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:165740 CAPLUS
DOCUMENT NUMBER: 110:165740
TITLE: B-cell restricted saporin immunotoxins: activity against B-cell lines and chronic lymphocytic leukemia cells
AUTHOR(S): Bregni, Marco; Siena, Salvatore; Formosa, Anna; Lappi, Douglas A.; Martineau, Darlene; Malavasi, Fabio; Dorken, Bernd; Bonadonna, Gianni; Gianni, Alessandro M.
CORPORATE SOURCE: Div. Med. Oncol., Ist. Naz. Tumori, Milan, 20133, Italy
SOURCE: Blood (1989), 73(3), 753-62
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
AB B cell-restricted immunotoxins were constructed by conjugating anti-B monoclonal antibodies to saporin, the major ribosome-inactivating protein from the seeds of the **plant** Saponaria officinalis. HD37-SAP is directed against CD19, the broadest B cell-specific determinant. HD36-SAP and HD6-SAP recognize 2 different epitopes on the CD22 mol., an antigen present on the cell surface of B cells at late stages of differentiation. All 3 immunotoxins inhibited DNA synthesis and protein synthesis in target **B lymphoma** cells with a dose-related effect, in short incubation times and in the absence of potentiators. A clonogenic assay demonstrated that all immunotoxins eliminated >2 log units of clonogenic malignant B cells with a 2-h incubation at concns. not toxic to cells not bearing target antigens. The immunotoxin activity was evaluated by DNA synthesis inhibition in fresh .beta.-chronic lymphocytic leukemia cells (B-CLL) stimulated to proliferate by incubation with an antibody specific for the receptor of C3b complement component (CR1) plus B cell growth factor. B-CLL cell DNA synthesis was actively inhibited by treatment at low immunotoxin concn. without need of potentiators.

Immunotoxins exerted their effect also in whole blood of CLL patients under conditions achievable in vivo. Thus, B cell-restricted immunotoxins HD37-SAP, HD39-SAP, and HD6-SAP are good candidates for in vivo therapy of .beta.-cell malignancies.

L2 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1988:431669 CAPLUS
DOCUMENT NUMBER: 109:31669
TITLE: Activity of a monoclonal antibody-saporin-6 conjugate against **B-lymphoma** cells
AUTHOR(S): Bregni, Marco; Lappi, Douglas A.; Siena, Salvatore; Formosa, Anna; Villa, Silvia; Soria, Marco; Bonadonna, Gianni; Gianni, A. Massimo
CORPORATE SOURCE: Div. Med. Oncol., Ist. Naz. Tumori, Milan, 20133, Italy
SOURCE: J. Natl. Cancer Inst. (1988), 80(7), 511-17
CODEN: JNCIEQ; ISSN: 0027-8874
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A monoclonal antibody reactive with the Ig heavy chain (TEC IgM) has been conjugated to saporin-6 (SAP), which is the major ribosome-inactivating protein from the seeds of the **plant** Saponaria officinalis. Studies with Burkitt's lymphoma cell line Bjab 113 demonstrate that this immunotoxin is capable of killing 3 logs (99.9%) of clonogenic lymphoma cells after a 2-h incubation. The presence of human bone marrow inhibits the activity of the conjugate. However, full potency of TEC IgM-SAP immunotoxin is restored by adding 1 mM amantadine to the incubation medium. The reaction is highly specific and is inhibited by the presence of excess anti-.mu.-antibody or human serum. Clonal growth of other Brukitt's lymphoma cell lines is inhibited to a lesser extent by the immunotoxin. The presence of surface IgM on the different cell lines is directly correlated to target cell killing by TEC IgM-SAP. Isolation of Bjab 113 clones surviving treatment demonstrates that only a minority are truly resistant and that the others randomly escape the treatment. The highly potent and specific activity of this conjugate in the presence of bone marrow buffer coat and its exceptionally rapid onset of action make this conjugate a good candidate for the ex vivo elimination of neoplastic cells from the bone marrow of non-Hodgkin's lymphoma patients.

L2 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:521473 CAPLUS
DOCUMENT NUMBER: 103:121473
TITLE: A comparison of established human lymphoma lines by flow cytometry: quantitation of Ricinus communis agglutinin binding and the effect of specific glycosidases
AUTHOR(S): Brossmer, Reinhard; Bohn, Burghard; Sauer, Anke; Zur Hausen, Harald
CORPORATE SOURCE: Inst. Biochem. II, Univ. Heidelberg, Heidelberg, D-6900, Fed. Rep. Ger.
SOURCE: Eur. J. Cancer Clin. Oncol. (1985), 21(7), 825-31
CODEN: EJCODS; ISSN: 0277-5379
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two established cell lines of human **B**-cell **lymphomas** derived from Burkitt lymphomas and their Epstein-Barr virus-transformed counterparts were analyzed with respect to their ability to bind the .beta.-galactoside-specific lectin Ricinus communis agglutinin. Native and sialidase- as well as sialidase-.beta.-galactosidase-treated cells were compared. The method for the quant. detn. of av. nos. of binding sites and of apparent affinity consts. was flow cytometry with fluorescence-labeled lectin. Although with native cells there was no deviation of the values for virus-transformed cells from those for the parent cells, some differences could be detected after glycosidase treatment.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:13:14 ON 04 FEB 2002)
L3 93 S L2
L4 37 S L3 AND (ANTIGEN OR VACCIN? OR IMMUNIZ? OR IMMUNIS?)
L5 24 DUP REM L4 (13 DUPLICATES REMOVED)

L5 ANSWER 1 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-596903 [67] WPIDS
DOC. NO. CPI: C2001-176650
TITLE: Novel polypeptide **vaccine** produced in **plants**, useful for inducing an immune response to a self-**antigen** on the surface of certain tumor cells.
DERWENT CLASS: B04 D16
INVENTOR(S): REINL, S J; TURPEN, T H
PATENT ASSIGNEE(S): (LARG-N) LARGE SCALE BIOLOGY CORP; (MCCO-I) MCCORMICK A A; (TUSE-I) TUSE D
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001068682	A1	20010920	(200167)*	EN	89

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001068682	A1	WO 2000-US28362	20001013

PRIORITY APPLN. INFO: US 2000-522900 20000310
AN 2001-596903 [67] WPIDS
AB WO 200168682 A UPAB: 20011119
NOVELTY - A polypeptide self-**antigen** (I) useful as a tumor-specific **vaccine** in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of the tumor, is new.

DETAILED DESCRIPTION - (I) includes an epitope or epitopes unique to, or over expressed by, cells of the tumor, thereby distinguishing the tumor from all other tumors of the same or different histological type, or in the subject or in another member of the subject's species. (I) is produced in a cell or organism that has been transformed or transfected with the nucleic acid derived from the tumor of the subject, is obtainable from the cell or organism in correctly folded form, without a need for denaturation and renaturation and mimics the epitope or epitopes in their native form. (I) is capable of inducing an immune response in a mammal, including the subject, without a need for adjvuant or other immunostimulatory materials, so that administration of the polypeptide results in an antibody or cell-mediated response to the epitope or epitopes.

INDEPENDENT CLAIMS are also included for the following:

(1) an individual-specific immunogenic product (II) comprising (I);

(2) a **vaccine** composition (VC) useful for inducing a tumor-specific immune response, idiotype-specific anti-lymphoma immune response, a polyclonal immune response to at least one idiotype of a surface immunoglobulin or a polyclonal immune response to an idiotype in a mouse, comprising (I); and

(3) producing (I).

ACTIVITY - Cytostatic; immunostimulator. The idiotype-bearing self **antigen** was administered by successive subcutaneous injection of 0.5 mg of the **antigen** and ISAF-1 adjuvant to humans with low grade **B**-cell **lymphoma**. The patients were given additional injections once a month for 5 months and booster doses were given annually. The results indicated that at least 6 of the 20 patients showed both immunological and clinical, including radiographic, signs of therapeutic success. The sera had significant titers of antibodies specific for the idiotype of their lymphoma cells and ScFV polypeptide used for **immunization**. Clinically, no signs of tumor progression and a statistically significant prolonged disease free interval after **vaccination** compared to historical controls, were observed. PCR (polymerase chain reaction) analysis of lymphocyte DNA across bcl-2/Igh, a molecular marker of human lymphoma, further confirmed the successful treatment of the lymphoma.

MECHANISM OF ACTION - Polyclonal anti-idiotypic antibody response inducer; cell-mediated immune response inducer (claimed).

USE - VC is useful for inducing a tumor-specific immune antibody response in a tumor-bearing subject or a subject who had a tumor e.g. **B**-cell **lymphoma**, and was treated so that no tumor is clinically or radiographically evident. (I) is useful for inducing a protective antitumor immune response (claimed).

ADVANTAGE - (I) can be produced at high levels, easy to purify and can be appropriately folded to mimic the conformation of the native epitopes displayed at the tumor cell surface.

Dwg.0/5

L5 ANSWER 2 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-316135 [33] WPIDS
DOC. NO. CPI: C2001-097326
TITLE: Novel library of dual-domain nucleic acid molecules useful for producing dual-domain proteins, or idiotypic scFv **vaccine** useful for

treating **B**-cell **lymphoma**.

DERWENT CLASS: B04 C06 D16
INVENTOR(S): LINDBO, J A; REINL, S J; TURPEN, T
PATENT ASSIGNEE(S): (LARG-N) LARGE SCALE BIOLOGY CORP
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001023543	A1	20010405	(200133)*	EN	77
AU 2000076017	A	20010430	(200142)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001023543	A1	WO 2000-US25965	20000922
AU 2000076017	A	AU 2000-76017	20000922

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000076017	A Based on	WO 2001023543

PRIORITY APPLN. INFO: US 1999-155978P 19990924
AN 2001-316135 [33] WPIDS
AB WO 200123543 A UPAB: 20010615
NOVELTY - A library (I) of dual-domain nucleic acid molecules, each having a first and a second domain that are separated and linked by a linker which is a member of a randomized library (RL) of linkers that vary in size and nucleotide sequence and consists of a repeated pattern (RP) of degenerate repeated triplet nucleotides, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a dual-domain nucleic acid molecule (II) selected from (I);

(2) a library (III) of dual-domain polypeptide molecules each described by the formula D1-L-D2, where D1 and D2 are polypeptide domains and L is a peptide or a polypeptide linker which is a member of RL;

(3) a library (IV) of multi-domain polypeptide molecules each comprising polypeptide domains D each pair of which is linked by a peptide or polypeptide linker L, each molecule being described by the formula DxLy, where x = 2-20 and y = 1-19, with the condition that for any value of x:

(i) y = x-1;

(ii) D1 is bonded to a single C-terminal linker;

(iii) the C-terminal-most D is bonded to a single N-terminal linker;

(iv) each of D2-D19 are bonded to a N-terminal and a C-terminal linker; and

(v) each L is a member of RL;

(4) a dual-domain polypeptide molecule (V) selected from (III);
(5) a multi-domain polypeptide molecule (VI) selected from (IV);
(6) generating (I);
(7) a population of dual-domain polypeptides (VIII) or a dual-domain polypeptide of the population, obtained by the above method;
(8) producing (V);
(9) a linker nucleic acid molecule or a sequence (IX) that joins two nucleic acid domains or two nucleic acid sequences encoding two polypeptide domains, which has a pattern of degenerate repeated triplet nucleotides, where all the three nucleotides at positions 1-3 are different, and the molecule or sequence that joins the domains does not encode Gly4Ser or its repeat;
(10) a library (X) of (IX); and
(11) making (X).

USE - (I) is useful for producing dual-domain proteins of interest that have therapeutic value, e.g., idiotypic scFv **vaccine** for treating **B**-cell **lymphoma**.

ADVANTAGE - The expression systems obtained by the above said methods are suitable for rapid and economical production of useful quantities of correctly folded polypeptides in surprisingly high abundance and potent immunogenicity.

Dwg.0/3

L5 ANSWER 3 OF 24 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001280645 EMBASE

TITLE: **Plant** viral genes in DNA idiotypic **vaccines** activate linked CD(4+) T-cell mediated immunity against B-cell malignancies.

AUTHOR: Savelyeva N.; Munday R.; Spellerberg M.B.; Lomonossoff G.P.; Stevenson F.K.

CORPORATE SOURCE: F.K. Stevenson, Molecular Immunology Group, Tenovus Laboratory, Southampton Univ. Hospitals Trust, Southampton S016 6YD, United Kingdom. ns1@soton.ac.uk

SOURCE: Nature Biotechnology, (2001) 19/8 (760-764).
Refs: 32
ISSN: 1087-0156 CODEN: NABIF

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB DNA delivery of tumor **antigens** can activate specific immune attack on cancer cells. However, **antigens** may be weak, and immune capacity can be compromised. Fusion of genes encoding activating sequences to the tumor **antigen** sequence facilitates promotion and manipulation of effector pathways. Idiotypic determinants of B-cell tumors, encoded by the variable region genes, are clone-specific tumor antigens. When assembled as single-chain Fv (scFv) alone in a DNA **vaccine**, immunogenicity is low. Previously, we found that fusion of a sequence from tetanus toxin (fragment C; FrC) promoted anti-idiotypic protection against lymphoma and myeloma. We have now investigated an alternative fusion gene derived from a **plant** virus, potato virus X coat protein, a primary antigen in

humans. When fused to scFv, the self-aggregating protein generates protection against lymphoma and myeloma. In contrast to scFv-FrC, protection against lymphoma is mediated by CD4(+) T cells, as is protection against myeloma. Plant viral proteins offer new opportunities to activate immunity against linked T-cell epitopes to attack cancer.

L5 ANSWER 4 OF 24 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002017834 EMBASE
TITLE: Patent alert.
AUTHOR: Banerjee D.; Tebbutt S.J.
CORPORATE SOURCE: D. Banerjee, Memorial Sloan Kettering Cancer Ctr., New York, NY, United States
SOURCE: Current Opinion in Molecular Therapeutics, (2001) 3/6 (518-521).
ISSN: 1464-8431 CODEN: CUOTFO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English

L5 ANSWER 5 OF 24 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:502754 SCISEARCH
THE GENUINE ARTICLE: 443XJ
TITLE: Production of anti-CD3 and anti-CD7 ricin A-immunotoxins for a clinical pilot study
AUTHOR: van Oosterhout Y V J M (Reprint); van Emst J L; Bakker H H; Preijers F W M B; Schattenberg A V M B; Ruiter D J; Evers S; Koopman J P; de Witte T
CORPORATE SOURCE: Univ Nijmegen, Med Ctr St Badboud, Dept Hematol, Geert Grootepl 8, NL-6525 GA Nijmegen, Netherlands (Reprint); Univ Nijmegen, Med Ctr St Badboud, Dept Hematol, NL-6525 GA Nijmegen, Netherlands; Univ Nijmegen, Med Ctr St Badboud, Dept Clin Pharm, NL-6525 GA Nijmegen, Netherlands; Univ Nijmegen, Med Ctr St Badboud, Dept Pathol, NL-6525 GA Nijmegen, Netherlands; Univ Nijmegen, Med Ctr St Badboud, Cent Anim Lab, NL-6525 GA Nijmegen, Netherlands
COUNTRY OF AUTHOR: Netherlands
SOURCE: INTERNATIONAL JOURNAL OF PHARMACEUTICS, (19 JUN 2001) Vol. 221, No. 1-2, pp. 175-186.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0378-5173.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 26
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This report describes the preparation of an immunotoxin-combination, consisting of an anti-CD3 and anti-CD7 monoclonal antibody (MoAb) both conjugated to the A-chain of **plant** toxin ricin, for the experimental treatment of graft-versus-host disease. MoAbs and toxin were conjugated by conventional biochemical

and chromatographic techniques. Raw materials, intermediate and final products were evaluated in accordance with the relevant 'points to consider' of the FDA. Yields, purity and sterility of the two final products were all satisfactory. Preservation of MoAb-affinity and toxin-activity were confirmed in biological assays. The LD50, 25-45 mg immunotoxin-combination/kg mouse, equalled that of similar immunotoxins already in clinical use. Because in vitro cross-reactivity screening revealed an unexpected binding of the CD3-MoAb to the esophagus epithelium, human doses of immunotoxin-combination were administered to two cynomolgus monkeys. Clinically relevant serum concentrations were obtained without irreversible toxicities occurring. The T-1/2 varied between similar to6 and 9 h and the C-max ranged from 1.8 to 3.9 mug/ml. The main side effect was a transient rise of serum creatine kinase. Importantly, neither damage nor binding of the CD3-immunotoxin to the monkey esophagus epithelium could be demonstrated. It was concluded that sufficient material of proper quality and with an acceptable toxicity profile was produced, warranting the evaluation in a clinical pilot-study.

L5 ANSWER 6 OF 24 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002022231 MEDLINE
DOCUMENT NUMBER: 21311492 PubMed ID: 11418304
TITLE: Specifically targeting the CD22 receptor of human **B**-cell **lymphomas** with RNA damaging agents.
AUTHOR: Newton D L; Hansen H J; Liu H; Ruby D; Iordanov M S; Magun B E; Goldenberg D M; Rybak S M
CORPORATE SOURCE: SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, Room 162, Building 567, Frederick, MD 21702-1201, USA.
CONTRACT NUMBER: CA-39360 (NCI)
ES-08456 (NIEHS)
NO1-CO-56000 (NCI)
SOURCE: CRITICAL REVIEWS IN ONCOLOGY/HEMATOLOGY, (2001 Jul-Aug) 39 (1-2) 79-86. Ref: 59
Journal code: 8916049. ISSN: 1040-8428.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011214

AB Targeting CD22 on human B-cells with a monoclonal antibody conjugated to a cytotoxic RNAse causes potent and specific killing of the lymphoma cells in vitro. This translates to anti-tumor effects in human lymphoma models in SCID mice. RNA damage caused by RNAses could be an important alternative to standard DNA damaging chemotherapeutics. Moreover, targeted RNAses may overcome problems of toxicity and immunogenicity associated with **plant** or bacterial toxin containing immunotoxins.

L5 ANSWER 7 OF 24 SCISEARCH

ACCESSION NUMBER: 2001:245137 SCISEARCH
THE GENUINE ARTICLE: 409BA
TITLE: Cowpea mosaic virus as a **vaccine** carrier of heterologous **antigens**
AUTHOR: Brennan F R (Reprint); Jones T D; Hamilton W D O
SOURCE: MOLECULAR BIOTECHNOLOGY, (JAN 2001) Vol. 17, No. 1, pp. 15-26.
Publisher: HUMANA PRESS INC, 999 RIVERVIEW DRIVE SUITE 208, TOTOWA, NJ 07512 USA.
ISSN: 1073-6085.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 104

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **plant** virus, cowpea mosaic virus (CPMV), has been developed as an expression and presentation system to display antigenic epitopes: derived from a number of **vaccine** targets including infectious disease agents and tumors. These chimeric virus particles (CVPs) could represent a cost-effective and safe alternative to live replicating virus and bacterial **vaccines**. A number of CVPs have now been generated and their immunogenicity examined ill a number of animal species. This review details the humoral and cellular immune responses generated by these CVPs following both par-enteral and mucosal delivery and highlights the potential of CVPs to elicit protective immunity from both viral and bacterial infection.

L5 ANSWER 8 OF 24 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999110954 MEDLINE
DOCUMENT NUMBER: 99110954 PubMed ID: 9892697
TITLE: Rapid production of specific vaccines for lymphoma by expression of the tumor-derived single-chain Fv epitopes in tobacco plants.
AUTHOR: McCormick A A; Kumagai M H; Hanley K; Turpen T H; Hakim I; Grill L K; Tuse D; Levy S; Levy R
CORPORATE SOURCE: Biosource Technologies, Inc., 3333 Vacavalley Parkway, Suite 1000, Vacaville, CA 95688, USA.
CONTRACT NUMBER: AI37219 (NIAID)
CA33399 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jan 19) 96, (2) 703-8.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990316

AB Rapid production of protein-based tumor-specific **vaccines** for the treatment of malignancies is possible with the **plant** -based transient expression system described here. We created a modified tobamoviral vector that encodes the idiotype-specific single-chain Fv fragment (scFv) of the immunoglobulin from the 38C13 mouse **B** cell **lymphoma**. Infected Nicotiana benthamiana **plants** contain high levels of secreted scFv

protein in the extracellular compartment. This material reacts with an anti-idiotype antibody by Western blotting, ELISA, and affinity chromatography, suggesting that the **plant**-produced 38C13 scFv protein is properly folded in solution. Mice **vaccinated** with the affinity-purified 38C13 scFv generate >10 micrograms/ml anti-idiotype immunoglobulins. These mice were protected from challenge by a lethal dose of the syngeneic 38C13 tumor, similar to mice **immunized** with the native 38C13 IgM-keyhole limpet hemocyanin conjugate **vaccine**. This rapid production system for generating tumor-specific protein **vaccines** may provide a viable strategy for the treatment of non-Hodgkin's lymphoma.

L5 ANSWER 9 OF 24 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999016458 EMBASE
TITLE: Approaches to new **vaccines**.
AUTHOR: Mahon B.P.; Moore A.; Johnson P.A.; Mills K.H.G.
CORPORATE SOURCE: B.P. Mahon, Infection and Immunity Group, National University of Ireland, Maynooth, County Kildare, Ireland
SOURCE: Critical Reviews in Biotechnology, (1998) 18/4 (257-282).
Refs: 161
ISSN: 0738-8551 CODEN: CRBTE5
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The explosive technological advances in the fields of immunology and molecular biology in the last 5 years had an enormous impact on the identification of candidate **vaccines** against diseases, which until a few years ago seemed uncontrollable. Increased knowledge of the immune system has helped to define the mechanisms that underlie successful **immunization** and is now being exploited to develop improved versions of existing **vaccines** and new **vaccines** against emerging pathogens, tumors, or autoimmune diseases. An understanding of the mechanisms of action of novel adjuvants and the development of new vector and delivery systems will have a major impact on **vaccine** strategies. The use of DNA encoding antigens from pathogenic viruses, bacteria, and parasites as **vaccines** is a new approach that is receiving considerable attention. This and other innovative approaches, including **vaccine** production in plants, are appraised in this review. The successful eradication of smallpox and the imminent eradication of poliomyelitis by worldwide **immunization** campaigns provide positive examples of how the **vaccine**-mediated approach can lead to disease elimination; with the advent of new **vaccines** and improved delivery systems, there is no scientific reason why these successes cannot be repeated.

L5 ANSWER 10 OF 24 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 97:734631 SCISEARCH

THE GENUINE ARTICLE: XY515
TITLE: Construction, expression, and characterization of BD1-G28-5 sFv, a single-chain anti-CD40 immunotoxin containing the ribosome-inactivating protein bryodin 1
AUTHOR: Francisco J A; Gawlak S L; Siegall C B (Reprint)
CORPORATE SOURCE: BRISTOL MYERS SQUIBB PHARMACEUT RES INST, DEPT MOL IMMUNOL, 3005 1ST AVE, SEATTLE, WA 98121 (Reprint); BRISTOL MYERS SQUIBB PHARMACEUT RES INST, DEPT MOL IMMUNOL, SEATTLE, WA 98121
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (26 SEP 1997) Vol. 272, No. 39, pp. 24165-24169.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The major limitation to the use of immunotoxins in the clinic is the toxicity associated with the toxin moiety, BD1-G28-5 single-chain Fv (sFv) is a single-chain immunotoxin targeted to human CD40 and consists of bryodin 1 (BD1), a **plant** ribosome-inactivating protein that is 20-30-fold less toxic in animals than commonly used toxins, fused to the sFv region of the anti-CD40 monoclonal antibody G28-5, This immunotoxin was expressed in Escherichia coli and purified from refolded inclusion bodies. BD1-G28-5 sFv retained the full protein synthesis inhibition activity of recombinant BD1 and specifically bound to CD40 with a binding affinity, k(d), of 1.5 nM, within 10-fold of the bivalent parental monoclonal antibody, BD1-G28-5 sFv was potently cytotoxic against CD40-expressing B lineage non-Hodgkin's lymphoma and multiple myeloma cell lines, with EC50 values in the ng/ml range, but not against a CD40-negative T cell line, Interestingly, BD1-G28-5 sFv was not cytotoxic against CD40-expressing carcinoma cell lines that were sensitive to a BD1-based immunotoxin conjugate targeted to the Le(y) carbohydrate **antigen**, These data represent the first report indicating that BD1 can be used in the construction of potent single-chain immunotoxins, Additionally, although BD1-G28-5 sFv effectively killed CD40-expressing hematologic malignancies, its lack of activity against CD40-expressing carcinomas suggests that CD40-mediated trafficking of BD1 differs in the two cancer types.

L5 ANSWER 11 OF 24 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998014568 MEDLINE
DOCUMENT NUMBER: 98014568 PubMed ID: 9354445
TITLE: Systemic therapy with 3BIT, a triple combination cocktail of anti-CD19, -CD22, and -CD38-saporin immunotoxins, is curative of human **B**-cell **lymphoma** in severe combined immunodeficient mice.
AUTHOR: Flavell D J; Noss A; Pulford K A; Ling N; Flavell S U
CORPORATE SOURCE: University Department of Pathology, Southampton General Hospital, Hampshire, United Kingdom.
SOURCE: CANCER RESEARCH, (1997 Nov 1) 57 (21) 4824-9.

Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19990129
Entered Medline: 19971120

AB We demonstrate in these preclinical studies that all severe combined immunodeficient mice injected with the human **B**-cell **lymphoma** cell line Ramos are cured when treated with a combination of anti-CD19, -CD22, and -CD38-saporin immunotoxins (ITs; termed 3BIT). Each component IT used individually did not cure the majority of animals but did significantly prolong their survival compared with PBS sham-treated controls, although the majority succumbed eventually to disease. The very significant improvement obtained with the three-IT combination 3BIT was not due to an antibody or antibody-plus-IT effect. We postulate that by targeting against these three cell surface molecules, we have effectively ensured delivery of saporin to each lymphoma cell with growth potential within the tumor, thus overcoming the problems of heterogeneity of target **antigen** expression that can limit the therapeutic efficacy of single-IT therapy or even two-IT combination therapy. These "proof of principle" findings have an obvious important bearing on antibody-based therapies for cancer and provide the rationale needed for the design and implementation of clinical trials with such combinations.

L5 ANSWER 12 OF 24 CANCERLIT
ACCESSION NUMBER: 97621906 CANCERLIT
DOCUMENT NUMBER: 97621906
TITLE: Construction and expression of BD1-G28-5 sFv, a single-chain immunotoxin targeted to CD40 (Meeting abstract).
AUTHOR: Gawlak S L; Francisco J A; Ledbetter A A; Siegall C B
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121 USA.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997). Vol. 38, pp. A566.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199711

AB Bryodin 1 (BD1) is a type I ribosomal inactivating protein (RIP) from the **plant** Bryonia dioica. It has potent cell-free protein synthesis inhibition activity but is relatively non-toxic in mice and rats with LD50 values more than 40 mg/kg in comparison to widely used toxins such as ricin A chain and saporin which have LD50 values less than 4 mg/kg. We have constructed a single-chain immunotoxin, BD1-G28-5 sFv, targeted to the CD40 **antigen**. CD40 is highly expressed on a wide range of hematologic malignancies and carcinomas. BD1-G28-5 sFv is cytotoxic to CD40-positive malignant **B**-cell **lymphomas** with EC50 values of 5-30 ng/ml. Specificity of the CD40-mediated activity was shown by the ability of G28-5 IgG to block the cytotoxic activity of the fusion toxin. Additionally, BD1-G28-5 sFv did not kill CD40-negative

T cell lines. Experiments detailing the antitumor activity of BD1-G28-5 sFv in vitro and in vivo against CD40-expressing malignancies are ongoing. Specific focus on the comparison between G28-5 sFv-PE40, a similar single-chain immunotoxin utilizing a binding defective form of Pseudomonas toxin, and BD1-G28-5 sFv will be presented to compare their respective therapeutic windows.

L5 ANSWER 13 OF 24 CANCERLIT
ACCESSION NUMBER: 97620975 CANCERLIT
DOCUMENT NUMBER: 97620975
TITLE: 3BIT, a triple combination cocktail of anti-CD19, -CD22 and -CD38-saporin immunotoxins is curative of human **B**-cell **lymphoma** in SCID mice (Meeting abstract).
AUTHOR: Flavell D; Noss A; Pulford K; Flavell S
CORPORATE SOURCE: The Simon Flavell Leukemia Research Unit, University of Southampton, UK.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997). Vol. 38, pp. A557.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
(CLINICAL TRIAL)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199710
AB One strategy to overcome the problem of heterogeneity of target **antigen** expression would be to target against multiple target **antigens** on the tumor cell surface. Using combinations of up to three immunotoxins (IT) we have conducted preclinical studies in a SCID mouse model of human lymphoma which prove this important principle and provide the rationale for implementing clinical trials in man. We used combinations of two and three saporin ITs, each with a different target **antigen** specificity (anti-CD19, -CD22 or CD38) in SCID mice bearing the human **B**-cell **lymphoma** cell line Ramos. A triple combination of all three immunotoxins, termed 3BIT, was 100% curative of SCID-Ramos mice, whilst a combination pair of anti-CD22 plus anti-CD38 immunotoxins cured 80% of the animals. Combination pairs of anti-CD19 plus -CD38 or anti-CD19 plus -CD22 IT's cured only 50% of the animals. Each of the three individual IT's used alone performed significantly less well than the various 2 and 3 combinations studied and could be ranked in order of therapeutic potency as CD22 more than CD38 more than CD19. Control groups showed that the significant therapeutic improvement obtained with combinations was not due to an antibody effect or to an antibody plus IT interaction.

L5 ANSWER 14 OF 24 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96388294 MEDLINE
DOCUMENT NUMBER: 96388294 PubMed ID: 8795695
TITLE: Response of **B**-cell **lymphoma** to a combination of bispecific antibodies and saporin.
AUTHOR: French R R; Bell A J; Hamblin T J; Tutt A L; Glennie M J
CORPORATE SOURCE: Lymphoma Research Unit, Tenovus Research Laboratory, Southampton General Hospital, U.K.
SOURCE: LEUKEMIA RESEARCH, (1996 Jul) 20 (7) 607-17.
Journal code: K9M; 7706787. ISSN: 0145-2126.

PUB. COUNTRY: ENGLAND: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 19961106
Entered Medline: 19961018

AB Observations are described using a combination of two bispecific F(ab')2 antibodies (BsAb) to deliver the ribosome-inactivating protein, saporin, in the treatment of low-grade, end-stage, **B**-cell **lymphoma**. Two BsAb were used, each having one arm directed at saporin and one at the CD22 on target B cells. The BsAb, however, recognized different, non-overlapping epitopes on each molecule, a strategy which permits high-avidity double attachment of saporin to the target. The BsAb and saporin were pre-mixed at a molar ratio of 3:1 24 h before treatment and infused intravenously over a period of 1 h. Five patients have been treated, mostly with weekly doses of between 2 and 4 mg of saporin for a period of up to 6 weeks. Toxicity was minimal. Three complained of weakness and myalgia for 1 to 2 days after treatment, without objective neurological deficit or rise in serum creatine kinase. One patient produced an anti-mouse Fab' and an anti-saporin response. All patients showed a rapid and beneficial response to treatment. When present, circulating tumor cells were cleared (4/4 patients), ascitic and pleural effusions were eliminated (2/2 patients) and one patient with splenomegaly showed a marked reduction in tumor bulk. Malignant lymph nodes showed significant, but partial, shrinkage in all patients and finally marrow responded well with tumor clearance in biopsy material and impressive resolution of pancytopenia in some patients. While these responses were mainly short-lived, with tumor progression once the treatment was stopped, their speed and magnitude, and the relative lack of associated toxicity warrants further study of this treatment to determine maximum tolerated doses and therapeutic utility.

L5 ANSWER 15 OF 24 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 95355155 MEDLINE
DOCUMENT NUMBER: 95355155 PubMed ID: 7543082
TITLE: Therapy of human **B**-cell **lymphoma** bearing SCID mice is more effective with anti-CD19- and anti-CD38-saporin immunotoxins used in combination than with either immunotoxin used alone.
AUTHOR: Flavell D J; Boehm D A; Emery L; Noss A; Ramsay A; Flavell S U
CORPORATE SOURCE: Simon Flavell Leukaemia Research Laboratory, Southampton General Hospital, UK.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1995 Jul 28) 62 (3) 337-44.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19990129

Entered Medline: 19950907

AB The CD19+ CD38+ human Burkitt's lymphoma cell line Ramos grows aggressively when injected intravenously (i.v.) into severe combined immunodeficient (SCID) mice, killing 100% of animals within a 33-42 day period with widely disseminated disease. Treatment commencing 7 days after i.v. injection of Ramos cells, with 3 doses of an anti-CD19 immunotoxin (IT; BU12-SAPORIN) or an anti-CD38IT (OKT10-SAPORIN) led to a significant prolongation of survival compared with sham-treated controls; the anti-CD38 IT gave the greatest prolongation of survival, but all treated animals eventually succumbed to disease. When both ITs were used in combination at equivalent dose levels, the therapeutic outcome was significantly improved over that obtained for single IT therapy, with 20% of animals surviving disease-free to 300 days. When anti-CD38 IT was given in combination with anti-CD19 antibody there was no therapeutic improvement over anti-CD38 IT used alone. However, when anti-CD19 IT was given in combination with CD38 antibody, a significant prolongation of survival ensued over that obtained with anti-CD19 IT alone, though this was not as significantly pronounced as that obtained when both ITs were used in combination and was only as good as the survival obtained with OKT10 antibody used alone. CD19 and CD38 are expressed on the surface of the vast majority of **B**-cell **lymphoma** and common acute lymphoblastic leukaemia cells, and our findings provide a sound rationale for a combination immunotoxin trial in these diseases directed against both these target molecules.

L5 ANSWER 16 OF 24 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 95341924 MEDLINE
DOCUMENT NUMBER: 95341924 PubMed ID: 7542357
TITLE: Treatment of **B**-cell **lymphomas** with combination of bispecific antibodies and saporin.
AUTHOR: French R R; Hamblin T J; Bell A J; Tutt A L; Glennie M J
CORPORATE SOURCE: Tenovus Research Laboratory, Southampton General Hospital, UK.
SOURCE: LANCET, (1995 Jul 22) 346 (8969) 223-4.
Journal code: LOS; 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19960129
Entered Medline: 19950822

AB We report the use of a bispecific F(ab')2 antibody to target the ribosome-inactivating protein saporin to the surface **antigen** CD22 in the treatment of low-grade, end-stage, **B**-cell **lymphoma**. Four patients were treated. Toxic effects were minimal (grade I), with mild fever, weakness, and myalgia for 1-2 days after treatment. One patient showed an antibody response to mouse Fab' and saporin. All patients showed rapid and beneficial responses to treatment with improvements in most disease sites and in peripheral blood cytopenia. The responses were short-lived (less than 28 days) but further study of this targeting system is warranted.

L5 ANSWER 17 OF 24 CANCERLIT
ACCESSION NUMBER: 95615298 CANCERLIT
DOCUMENT NUMBER: 95615298
TITLE: The recruitment of a ribosomal inactivating protein or T cells by antibody derivatives in the treatment of **B** cell **lymphoma**.
AUTHOR: Mcbride H M
CORPORATE SOURCE: Univ. of Southampton, United Kingdom.
SOURCE: Diss Abstr Int [C], (1994). Vol. 55, No. 4, pp. 1122. ISSN: 0419-4217.
DOCUMENT TYPE: (THESIS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199511
AB An idiotope associated with the surface IgM of a little studied murine **B** cell **lymphoma** (A31) was used as a highly specific target for immunotherapeutic studies. The A31 IgM was recovered by somatic fusion of the A31 tumor cells and a murine plasmacytoma, NS-1, producing a hybridoma that secreted pentameric A31 IgM in culture (rescued idiotypic IgM). A xenogenic fusion using a murine plasmacytoma line and splenocytes from a rat **immunized** with idiotypic IgM led to the successful isolation of anti-idiotypic monoclonal antibodies. A rat IgG2a designated Mc39-16, was chosen for detailed immunotherapeutic studies. Scatchard plot analysis of radioiodinated Mc39-16 binding to A31 cells produced a functional association constant of 3.8 x 0.8 M(-1) and enumerated the surface IgM molecules of A31 cells at approx 3 x105. Growth of the tumor was restricted initially to the B cell areas of the spleen. General invasion of splenic tissue occurred between 10 and 15 days post inoculation, at which time significant liver involvement was manifest. Coincident with the latter was a rapid rise in serum idiotype levels from less than 10 ug/ml to a maximum level of approx 70 ug/ml immediately prior to death. Therapy with Mc39-16 given 24 hr after tumor inoculation yielded long-term survivors in animals receiving less than 5 x 10(3) cells but limited survival of animals given greater than 2.5 x 104. The ribosome-inactivating protein saporin was delivered to the tumor cells in vitro using either an immunotoxin (IT) or bispecific F(ab')2 (antitumor x antisaporin) antibodies constructed using Mc39-16. The IT and one of the F(ab')2 constructs enhanced the toxicity of saporin by 1800- to 2900-fold. Despite this, the IT was capable of curing mice injected with the tumor while the bispecific antibodies gave only marginal therapeutic benefit. These studies demonstrate that A31 is likely to be a highly suitable model for the study of new immunotherapeutic treatments for human lymphoma. (Abstract shortened by UMI.) (Full text NOT AVAILABLE FROM UNIVERSITY MICROFILMS INTERNATIONAL)

L5 ANSWER 18 OF 24 CANCERLIT
ACCESSION NUMBER: 96625486 CANCERLIT
DOCUMENT NUMBER: 96625486
TITLE: Radiolabeled antibody therapy of lymphomas.
AUTHOR: Press O W; Eary J F; Appelbaum F R; Bernstein I D
CORPORATE SOURCE: University of Washington and the Fred Hutchinson Cancer Research Center, Seattle, WA.
SOURCE: Biol Ther Cancer Updates, (1994). Vol. 4, No. 4, pp. 1-13.

ISSN: 1056-3903.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199606

AB Cytotoxic drugs, toxins, and radionuclides may be targeted to malignant cells by linking them to monoclonal antibodies that recognize tumor-associated **antigens**. This overview first discusses the types of monoclonal antibodies, immunoconjugates and procedures that have been used to improve upon the poor results seen with unmodified monoclonal antibodies. These include sequential administration of chlorambucil, interferon-alpha, or interleukin-2, the use of engineered chimeric or humanized antibodies containing human Fc constant regions, and construction of bi-specific monoclonal antibodies. Cytotoxic agents include **plant** and bacterial toxins such as ricin A-chain, abrin, and Diphtheria toxin, chemotherapeutic drugs, and most promising, radionuclides in radioimmunotherapy. The selection of appropriate tumor types (lymphomas have the best known tumor-specific **antigens** and are most likely to benefit, but early trials have mainly involved hepatomas and melanomas) for radioimmunotherapy is discussed, as are the choices of target **antigen** and antibody. The **antigens** on **B**-cell **lymphomas** are tabulated together with their percent expression (50-95%) and susceptibility to endocytosis; CD19 is an excellent target, while many others are expressed on a variety of normal cell types or are not internalized. However, the actual choice of target **antigen** depends on many factors including whether radionuclides or toxins are to be in the conjugate, and practical details of conjugate formation. The potential radionuclides are reviewed as regards their physical properties and limitations. Iodine-131 has been most extensively used , but conjugates may be dehalogenated in vivo and energetic gamma-radiation presents potential risk to users. Yttrium-90 holds promise for radioimmunotherapy, but the absence of gamma emissions prevents its application in scintigraphy, for which conversely, indium-111 is very suitable. Rhenium-186, with beta-energy intermediate between I-131 and Y-90 is suitable for both scintigraphy and radioimmunotherapy. Other radionuclides, astatine-211, bismuth-212, and iodine-125 are discussed briefly. Treatment schedules and imaging studies with conjugates are covered, as is radioimmunotherapy with non-myeloablative doses of radioactivity. A table presents data for 11 non-myeloablative, and 2 myeloablative clinical trials of radioimmunotherapy in lymphomas, 7 of which were of B-cell non-Hodgkin's type. The Seattle study design, presented in more detail, involves categorization as 'favorable' or 'unfavorable' based on the results of trace-labeled infusions targeted to the CD20 or CD37 **antigens**. Patients in the 'favorable' category received therapeutic doses of I-131 labeled antibody (0.5-10 mg/kg; 232-777 mCi; delivering target doses of 1,000-3,075 cGy). The impact of spleen size, tumor burden and toxicity were discussed. Of 28 patients with B-cell non-Hodgkin's lymphomas, there were 15 complete and 3 partial responses among 20 patients given B1(CD20) antibody, 6 complete responses of 6 given MB1 (CD37), a complete response in one given anti-idiotype antibody, and a partial response in one case given IF5 (CD20) antibody. Future developments are discussed in light of these promising results. (105 References)

L5 ANSWER 19 OF 24 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 93306634 MEDLINE
DOCUMENT NUMBER: 93306634 PubMed ID: 7686448
TITLE: Delivery of saporin to human **B**-cell **lymphoma** using bispecific antibody: targeting via CD22 but not CD19, CD37, or immunoglobulin results in efficient killing.
AUTHOR: Bonardi M A; French R R; Amlot P; Gromo G; Modena D; Glennie M J
CORPORATE SOURCE: Lymphoma Research Unit, Tenovus Laboratory, General Hospital, Southampton, United Kingdom.
SOURCE: CANCER RESEARCH, (1993 Jul 1) 53 (13) 3015-21.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19980206
Entered Medline: 19930730

AB A panel of bispecific F(ab')2 antibodies (BsAb) have been constructed for delivering the ribosome-inactivating protein saporin to human **B** cell **lymphoma**. Each derivative was prepared with specificity for saporin and CD19, CD22, CD37, or immunoglobulin. In vitro studies measuring inhibition of [3H]leucine uptake by cultured Daudi and Raji cells demonstrated that, despite all BsAb capturing saporin on the cell surface, BsAb targeting through CD22 were far more cytotoxic than those functioning via CD19, CD37, or surface immunoglobulin. This exceptional activity of the CD22-specific BsAb appears to derive from its ability to deliver and accumulate saporin inside the target cells. Further studies showed that four CD22-specific BsAb all performed with equal potency and were able to increase saporin toxicity (50% inhibitory concentration) up to 1000-fold, from 2 x 10(-7) M to 2 x 10(-10) M. Pairs of anti-CD22 BsAb which recognized different nonblocking epitopes on the saporin molecule were able to bind saporin more avidly to the target cell and, as a consequence, increased cytotoxicity by at least an additional 10-fold, resulting in 50% inhibitory concentration for protein synthesis of 2 x 10(-11) M. These results suggest that selected combinations of BsAb which bind cooperatively to a toxin and the cell surface may provide an efficient way of delivering toxins to unwanted cells in patients.

L5 ANSWER 20 OF 24 EMBASE
ACCESSION NUMBER: 93209521 EMBASE
DOCUMENT NUMBER: 1993209521
TITLE: Rationale for the clinical use of immunotoxins: Monoclonal antibodies conjugated to ribosome-inactivating proteins.
AUTHOR: Preijers F.W.M.B.
CORPORATE SOURCE: Department of Hematology, University Hospital St Radboud, 8 Geert Grooteplein,6525 GA Nijmegen, Netherlands
SOURCE: Leukemia and Lymphoma, (1993) 9/4-5 (293-304).
ISSN: 1042-8194 CODEN: LELYEA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The use of chemotherapeutic drugs in combination with bone marrow transplantation to treat cancer patients has markedly improved the disease-free survival and cure rate. Part of the tumor cells, however, can escape from therapy due to resistance. Tumor-specific delivery of toxins that do not interfere with conventional drugs and are not yet cycle dependent seems to be a reasonable approach to overcome this problem. Natural ribosome-inhibiting-proteins (RIPs) from **plants**, bacteria and fungi which are extremely toxic inhibitors of protein synthesis are isolated and coupled to monoclonal antibodies (MoAbs) and receptor-specific ligands, immunotoxins (ITs), to fulfil this purpose. ITs are very suitable to eliminate malignant cells in vitro and in vivo. RIPs contain two or three active sites: a binding site which can be absent in a part of the RIPs and can be replaced by the MoAb; a translocation site that facilitates transport into the cytosol after internalization, and a cytotoxic site that enzymatically inhibits protein synthesis. Binding site containing toxins induce strong nonspecific cytotoxicity when coupled to MoAbs. Recent developments in recombinant DNA techniques enable genomic elimination of the binding site to reduce nonspecific cytotoxicity of these toxins. In this review the structures and mechanisms of action of RIPs as well as factors that influence cytotoxicity of immunotoxins are discussed. Moreover the problems dealing with in vivo application of ITs such as blood clearance by instability of the IT and hepatic entrapment, and production of antibodies directed against MoAb and toxin are reviewed.

L5 ANSWER 21 OF 24 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 93:102155 SCISEARCH
THE GENUINE ARTICLE: KL896
TITLE: IDIOTYPES OF PREEXISTING HUMAN ANTI-CARCINOMA ANTI-T AND ANTI-TN ANTIBODIES
AUTHOR: ZANETTI M (Reprint); LENERT G; SPRINGER G F
CORPORATE SOURCE: UNIV CALIF SAN DIEGO, DEPT MED, 225 DICKINSON ST, SAN DIEGO, CA, 92103 (Reprint); UHS, CHICAGO MED SCH, DEPT MICROBIOL IMMUNOL, HEATHER MARGARET BLIGH CANC RES LABS, N CHICAGO, IL, 60064; UNIV CALIF SAN DIEGO, CTR CANC, SAN DIEGO, CA, 92103; NORTHWESTERN UNIV, CTR CANC, CHICAGO, IL, 60611; UHS, CHICAGO MED SCH, DEPT SURG, CHICAGO, IL, 60064
COUNTRY OF AUTHOR: USA
SOURCE: INTERNATIONAL IMMUNOLOGY, (FEB 1993) Vol. 5, No. 2, pp. 113-119.
ISSN: 0953-8178.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 65

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB All humans normally possess antibodies, predominantly IgM, that react specifically with the Thomsen - Friedenreich (T) and the Tn **antigens** which are present in immunoreactive form on >85% of all human carcinomas, but not in healthy and otherwise diseased

tissues. We report here a serological study of idiotype expression and **antigen** reactivity of the anti-T and anti-Tn antibodies. Idiotypy was analyzed with rabbit antibodies raised against, and made specific for, affinity-purified polyclonal anti-T and anti-Tn antibodies from blood group A,B healthy adult donors. Anti-T and anti-Tn antibodies cross-reacted idiotypically in spite of their distinct epitope specificities. By adsorbing anti-T antibodies on insolubilized synthetic T carbohydrate we could firmly link idiotype expression with **antigen** reactivity. The relation of idiotype expression to the **antigen**-binding site of **plant** seed lectins was also studied; one originated from Arachis hypogaea [peanut agglutinin (PNA)], the other from Artocarpus integrifolia (Jacalin). PNA inhibited only anti-T antibodies. Jacalin inhibited both anti-T and anti-Tn antibodies in a dose-dependent manner. Neither idiotypic nor anti-idiotypic antibodies diminished the binding of lectins to T and Tn epitopes. The shared idiotypes on natural anti-T and anti-Tn antibodies permit consideration of application of their anti-idiotypes in treatment and/or prevention of human carcinoma.

L5 ANSWER 22 OF 24 CANCERLIT
ACCESSION NUMBER: 94697528 CANCERLIT
DOCUMENT NUMBER: 94697528
TITLE: Treatment of human lymphoma with saporin delivered by bispecific antibody (Meeting abstract).
AUTHOR: Glennie M J; French R R
CORPORATE SOURCE: Univ. of Southampton, Tenovus Lab., General Hosp., Southampton SO9 4XY, UK.
SOURCE: Non-serial, (1993). EACR-12, pp. 12th Biennial Meeting of the European Association for Cancer Research. April 4-7, 1993, Brussels, Belgium, 1993. :.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199411
AB We have constructed bispecific antibodies (BsAb) comprising two monoclonal Fab'gamma fragments linked at their hinges by tandem thioether bonds. In the present use, one Fab' arm is directed to the CD22 **antigen** present on many **B**-cell **lymphomas**, the other to an epitope on the type-1 ribosome-inactivating protein, saporin. Preliminary work in animals indicated that an efficient means of delivering intact saporin to tumor consists of injecting immune complexes formed by pre-mixing saporin in vitro with two BsAb--each having the same antitumor arm but different antisaporin arms directed against nonoverlapping epitopes. Delivery of such complexes to the cell surface leads to saporin being held there by the tenacious twin grip of two antibodies. Work in vitro with human cell lines revealed CD22 to be a highly efficient **antigen** for mediating saporin toxicity. Five patients with end-stage low-grade lymphoma have been treated with these toxin-antibody complexes, at saporin doses up to 5 mg weekly. Toxicity was minimal. Three patients experienced local inflammation over the vein used for the infusion. Two complained of weakness and myalgia, without objective neurological deficit or rise in serum creatine kinase. One produced antibodies to mouse Ig, but no antisaporin antibodies were detected. All patients experienced some beneficial response. Where present, tumor cells were cleared

from the blood. Ascites and pleural effusions were eliminated in the two patients exhibiting them. One patient showed a marked reduction in splenomegaly and two a reduction in lymph node size. However, no patient showed a resolution of all tumor, and large nodal masses remained resistant to the doses employed. Tumor in the marrow appeared to respond well, as there was impressive resolution of marked pancytopenia whenever present.

L5 ANSWER 23 OF 24 CANCERLIT
ACCESSION NUMBER: 92677839 CANCERLIT
DOCUMENT NUMBER: 92677839
TITLE: IMMUNOTOXIN THERAPY OF **B**-CELL **LYMPHOMA** (MEETING ABSTRACT).
AUTHOR: Stone M; Amlot P; Fay J; Till M; Ghetie V; Collins R; Tong A; May R; Newman J; Clark P; et al
CORPORATE SOURCE: Baylor-Sammons Cancer Center, Dallas, TX.
SOURCE: Blood, (1990). Vol. 76, No. 10, Suppl. 1, pp. 347a. ISSN: 0006-4971.
DOCUMENT TYPE: (CLINICAL TRIAL)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199203

AB Ricin is a **plant** toxin containing two disulfide-bonded polypeptide chains (A-B). The A chain is an enzyme which inactivates ribosomes and the B chain is a galactose-specific lectin which binds to all eukaryotic cells. Immunotoxins (ITs) are cell-reactive antibodies or ligands which are covalently coupled to holotoxins or their A chains. We have used ITs whose antibody portion is directed against molecules on neoplastic B cells from humans or mice coupled to ricin A chain. We have initiated studies to treat refractory **B**-cell **lymphomas** in humans with anti-CD22-A ITs and selected a CD22 antibody which recognizes only B cells in a panel of over 40 normal human tissues. When attached to ricin A chain via a linker containing a hindered disulfide bond (SMPT), the IT is 10-20-fold more toxic than ricin itself to the B-lymphoblastoid line, Daudi. Fab' fragments of the CD22 antibody linked via native cysteine residues to deglycosylated A chain (dgA) are as toxic as ricin to Daudi cells. The Fab'-As have the advantage of small size which can more easily penetrate solid tissues and the IgG-As have the advantage of longer in vivo half-life. Both anti-CD22-A IT constructs (IgG-SMPT-dgA and Fab'-dgA) received FDA approval for a Phase I clinical trial. To date, 26 patients (pts) have been treated; 23 with NHL and the remainder with PLL, CLL or CML in ALL crisis. Dose-related toxicities include vascular leak syndrome, myalgia and low-grade fever and dose-limiting toxicities include aphasia, pulmonary edema and rhabdomyolysis. The MTD for the Fab'-dgA is 75 mg/m2. Only one pt made antibody to ricin A chain and none made HAMA. With respect to clinical response, 40% of the pts achieved PR at 1 mo. In the subset of 11 pts whose tumor cells were greater than 50% CD22+, 73% achieved a PR at 1 wk and 55% at 1 mo. These results indicate that a B cell-specific immunotoxin can be administered safely to refractory **B lymphoma** pts at doses which kill significant numbers of tumor cells.

L5 ANSWER 24 OF 24 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 89135006 MEDLINE
DOCUMENT NUMBER: 89135006 PubMed ID: 2465042
TITLE: B-cell restricted saporin immunotoxins: activity

against B-cell lines and chronic lymphocytic leukemia cells.

AUTHOR: Bregni M; Siena S; Formosa A; Lappi D A; Martineau D; Malavasi F; Dorken B; Bonadonna G; Gianni A M

CORPORATE SOURCE: Division of Medical Oncology, Istituto Nazionale Tumori, Milano, Italy.

SOURCE: BLOOD, (1989 Feb 15) 73 (3) 753-62.
Journal code: A8G; 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198903

ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890329

AB B cell-restricted immunotoxins were constructed by conjugating anti-B monoclonal antibodies to saporin, the major ribosome inactivating protein from the seeds of the **plant** Saponaria officinalis. HD37-SAP is directed against CD19, the broadest B cell-specific determinant. HD39-SAP and HD6-SAP recognize two different epitopes on the CD22 molecule, an **antigen** present on the cell surface of B cells at late stages of differentiation. All three immunotoxins inhibited DNA synthesis and protein synthesis in target **B lymphoma** cells with a dose-related effect, in short incubation times and in the absence of potentiators. A clonogenic assay demonstrated that all immunotoxins could eliminate more than two logs of clonogenic malignant B cells with a two-hour incubation at concentrations not toxic to cells not bearing target **antigens**. The immunotoxin activity was evaluated by DNA synthesis inhibition in fresh B-chronic lymphocytic leukemia cells (B-CLL) stimulated to proliferate by incubation with an antibody specific for the receptor of C3b complement component (CR1) plus B cell growth factor. B-CLL cell DNA synthesis was actively inhibited by treatment at low immunotoxin concentration without need of potentiators. Immunotoxins exerted their effect also in whole blood of CLL patients under conditions achievable in vivo. We conclude that B cell-restricted immunotoxins HD37-SAP, HD39-SAP, and HD6-SAP are good candidates for in vivo therapy of B-cell malignancies.

(FILE 'MEDLINE' ENTERED AT 12:19:45 ON 04 FEB 2002)

```
L6          5099 SEA FILE=MEDLINE ABB=ON  PLU=ON  "LYMPHOMA, B-CELL"/CT
L9         47647 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIGENS/CT
L10           15 SEA FILE=MEDLINE ABB=ON  PLU=ON  L6 AND L9


L6          5099 SEA FILE=MEDLINE ABB=ON  PLU=ON  "LYMPHOMA, B-CELL"/CT
L11         5496 SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINES/CT
L12        30143 SEA FILE=MEDLINE ABB=ON  PLU=ON  IMMUNIZATION/CT
L13           22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L6 AND (L11 OR L12)
L14        57624 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIBODIES/CT
L15            2 SEA FILE=MEDLINE ABB=ON  PLU=ON  L13 AND L14

L16           17 L10 OR L15

L16  ANSWER 1 OF 17     MEDLINE
AN   2001483107     MEDLINE
```

TI Autoimmunity and lymphoma: tribulations of B cells.
AU Mackay I R; Rose N R
SO Nat Immunol, (2001 Sep) 2 (9) 793-5.
Journal code: D0G; 100941354. ISSN: 1529-2908.

L16 ANSWER 2 OF 17 MEDLINE
AN 2001212233 MEDLINE
TI Somatic hypermutation and B-cell lymphoma.
AU Dunn-Walters D; Thiede C; Alpen B; Spencer J
SO PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON. SERIES B: BIOLOGICAL SCIENCES, (2001 Jan 29) 356 (1405) 73-82. Ref: 72
Journal code: P5Z; 7503623. ISSN: 0962-8436.
AB During the B-cell response to T-cell-dependent antigens, the B cells undergo a rapid proliferative phase in the germinal centre. This is accompanied by the introduction of mutations into the immunoglobulin (Ig) variable region (V) genes. The B cells are then selected according to the affinity of the encoded immunoglobulin for antigen, resulting in affinity maturation of the response. Analysis of mutations in IgV genes has given insight into the history of individual B cells and their malignancies. In most cases, analysis of mutations confirms classifications of B-cell lineage designated by studies of cellular morphology and surface antigen expression. However, of particular interest is the subdivision of groups of malignancies by analysis of somatic hypermutation. It is now apparent that there are two subsets of chronic lymphocytic leukaemia (CLL), one with a low load of mutations and poor prognosis. and one with a heavy load of mutations with a much more favourable prognosis. In addition, in Burkitt's lymphoma, sporadic and endemic subtypes are now considered possibly to have a different pathogenesis, reflected in differences in the numbers of mutations. Hodgkin's disease, which was a mystery for many years, has now been shown to be a B-cell tumour. Although in many cases the Ig genes are crippled by somatic hypermutation, it is thought that failure to express Ig is more likely to be associated with problems of transcription. It has been proposed that the distribution of mutations in a B-cell lymphoma can be used to determine whether a lymphoma is selected. We have investigated the load and distribution of mutations in one group of lymphomas--marginal zone B-cell lymphomas of mucosa-associated lymphoid tissues (MALT-type lymphoma), which are dependent on Helicobacter pylori for disease progression, to investigate the limits of information that can be derived from such studies. Comparison of the load of mutations demonstrates that these tumours have approximately the same load of mutations as normal mucosal marginal zone B cells from the Peyer's patches and mucosal plasma cells. This is consistent with the origin of these cells from mucosal marginal zone B cells with plasma cell differentiation. To investigate selection in MALT lymphomas we compared a region of the framework region three in ten MALT lymphomas which use the V(H4) family, with the same codons in groups of V(H4) genes that are out of frame between V and J. The latter accumulate mutations but are not used and are not selected. A group of V(H4) genes are in-frame between V and J were also included for comparison. There were no obvious differences in the distribution of mutations between the groups of genes; the same hot spots and cold spots were apparent in each. In the MALT lymphomas, selection was apparent in the framework regions only and the tendency was to conserve. We therefore feel that there is selection to conserve antibody structure and that this does not reflect selection for

antigen. We do not believe that antigen selection can be deduced reliably from sequence information alone. It is possible that somatic hypermutation could be a cause of malignancy since it has been shown that the process may generate DNA strand breaks and is known to be able to generate insertions and deletions. Such events may mediate the translocation of genes--a process that is pivotal in the evolution of many lymphomas.

L16 ANSWER 3 OF 17 MEDLINE
AN 2000390037 MEDLINE
TI The hepatocyte growth factor/Met pathway in development, tumorigenesis, and B-cell differentiation.
AU van der Voort R; Taher T E; Derksen P W; Spaargaren M; van der Neut R; Pals S T
SO ADVANCES IN CANCER RESEARCH, (2000) 79 39-90. Ref: 506
Journal code: 2J6; 0370416. ISSN: 0065-230X.
AB This article summarizes the structure, signal transduction and physiologic functions of the HGF/Met pathway, as well as its role in tumor growth, invasion, and metastasis. Moreover, it highlights recent studies indicating a role for the HGF/Met pathway in antigen-specific B-cell development and B-cell neoplasia.

L16 ANSWER 4 OF 17 MEDLINE
AN 2000345414 MEDLINE
TI Expression of T-cell-associated antigens in B-cell non-Hodgkin's lymphoma.
AU Inaba T; Shimazaki C; Sumikuma T; Okano A; Hatsuse M; Okamoto A; Takahashi R; Ashihara E; Hibi S; Sudo Y; Yamagata N; Murakami S; Rin K; Fujita N; Yoshimura M; Nakagawa M
SO BRITISH JOURNAL OF HAEMATOLOGY, (2000 Jun) 109 (3) 592-9.
Journal code: AXC; 0372544. ISSN: 0007-1048.
AB We performed the immunophenotyping of 101 patients with B-cell non-Hodgkin's lymphoma (B-NHL) using two-colour flow cytometry (FCM) and found that lymphoma cells coexpressed at least one kind of T-cell-associated antigen (T-Ag; CD2, CD5, CD7) in 25 patients (24.8%). Among these three T-Ags, CD5 was the most frequently expressed, in 21 patients (20.8%), followed by CD7, expressed in five patients (5.0%), and CD2, which was expressed in two patients (2.0%). Two kinds of T-Ag were simultaneusly expressed in three patients (CD2/CD5, CD2/CD7, and CD5/CD7, each expressed in one patient). Concerning the expression pattern of T-Ag, there were no significant differences between lymph nodes and extranodal organs in the three patients with T-Ag-positive B-NHL (T-Ag(+) B-NHL) who were analysed. When comparing the clinical features between T-Ag(+) B-NHL and T-Ag-negative B-NHL (T-Ag(-) B-NHL), extranodal involvement and higher International Prognostic Index (H and H.I.) were significantly frequent in the former subgroup (P = 0.0119 and P = 0.0302 respectively).

L16 ANSWER 5 OF 17 MEDLINE
AN 2000292337 MEDLINE
TI Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma.
AU Feuring-Buske M; Buske C; Unterhalt M; Hiddemann W
SO ANNALS OF HEMATOLOGY, (2000 Apr) 79 (4) 167-74. Ref: 80
Journal code: A2P; 9107334. ISSN: 0939-5555.
AB Substantial advances in antigen-targeted lymphoma therapy have been achieved in recent years that make the use of monoclonal antibodies

a highly attractive concept and promise further improvements in the clinical management of malignant lymphoma. The development of the chimeric anti-CD20 antibody IDEC-C2B8 (Rituximab) proved the concept of an effective therapy with a single unconjugated monoclonal antibody in lymphoma patients. Radioimmunoconjugates with myeloablative activity induced response rates of 80-100% in heavily pretreated patients. Progress in the genetic engineering of immunotoxins has improved the efficacy of these constructs. Ongoing prospective clinical trials will define the optimal use of these innovative therapeutic agents in patients with malignant lymphoma, and may establish therapeutic strategies with a high anti-lymphoma specificity and a low unspecific toxicity.

L16 ANSWER 6 OF 17 MEDLINE
AN 1999061792 MEDLINE
TI Immunotherapy of B-cell lymphoma with CD3x19 bispecific antibodies: costimulation via CD28 prevents "veto" apoptosis of antibody-targeted cytotoxic T cells.
AU Daniel P T; Kroidl A; Kopp J; Sturm I; Moldenhauer G; Dorken B; Pezzutto A
SO BLOOD, (1998 Dec 15) 92 (12) 4750-7.
Journal code: A8G; 7603509. ISSN: 0006-4971.
AB Bispecific antibodies (CD3x19) against the CD3epsilon-chain of the T-cell-receptor/CD3 complex and the CD19 antigen on B cells can target polyclonal, nontumor-specific T cells to B lymphoma cells. This induces T-cell activation, and generation of cytotoxic T cells (CTLs). These polyclonal CTLs, targeted by the CD3x19 bispecific antibodies, can lyse CD19(+) B-lymphoma cells. In a xenotransplant model in severe combined immunodeficiency deficient (SCID) mice, we and others observed that CD28 triggering is required for efficient elimination of B-lymphoma cells and cure from the tumor in addition to CD3x19 administration. We also showed that the activation and targeting of CTLs to the target cell by signal one alone, ie, the CD3x19 mab, induces T-cell death by apoptosis. In blocking experiments we showed that this "veto" apoptosis is mediated by the CD95/Fas ligand. Addition of anti-CD28 (signal 2) renders the T cells resistant for veto apoptosis both in vitro and in vivo. We therefore conclude that the role of costimulation in immunotherapy with bispecific antibodies or other T-cell-based immune strategies is not only to facilitate T-cell activation but also to prevent T-cell deletion by apoptosis.

L16 ANSWER 7 OF 17 MEDLINE
AN 1999025947 MEDLINE
TI Immunostimulatory CpG oligodeoxynucleotides enhance the immune response to vaccine strategies involving granulocyte-macrophage colony-stimulating factor.
AU Liu H M; Newbrough S E; Bhatia S K; Dahle C E; Krieg A M; Weiner G J
SO BLOOD, (1998 Nov 15) 92 (10) 3730-6.
Journal code: A8G; 7603509. ISSN: 0006-4971.
AB Immunostimulatory oligodeoxynucleotides containing the CpG motif (CpG ODN) can activate various immune cell subsets and induce production of a number of cytokines. Prior studies have demonstrated that both CpG ODN and granulocyte-macrophage colony-stimulating factor (GM-CSF) can serve as potent vaccine adjuvants. We used the 38C13 murine lymphoma system to evaluate the immune response to a combination of these two adjuvants. Immunization using antigen, CpG ODN, and soluble GM-CSF enhanced production of antigen-specific

antibody and shifted production towards the IgG2a isotype, suggesting an enhanced TH1 response. This effect was most pronounced after repeat immunizations with CpG ODN and antigen/GM-CSF fusion protein. A single immunization with CpG ODN and antigen/GM-CSF fusion protein 3 days before tumor inoculation prevented tumor growth. CpG ODN enhanced the production of interleukin-12 by bone marrow-derived dendritic cells and increased expression of major histocompatibility complex class I and class II molecules, particularly when cells were pulsed with antigen/GM-CSF fusion protein. We conclude that the use of CpG ODN in combination with strategies involving GM-CSF enhances the immune response to antigen and shifts the response towards a TH1 response and that this approach deserves further evaluation in tumor immunization approaches and other conditions in which an antigen-specific TH1 response is desirable.

L16 ANSWER 8 OF 17 MEDLINE
AN 1998230467 MEDLINE
TI CpG DNA rescue from anti-IgM-induced WEHI-231 B lymphoma apoptosis via modulation of I kappa B alpha and I kappa B beta and sustained activation of nuclear factor-kappa B/c-Rel.
AU Yi A K; Krieg A M
SO JOURNAL OF IMMUNOLOGY, (1998 Feb 1) 160 (3) 1240-5.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
AB Unmethylated CpG dinucleotides in particular base contexts in oligonucleotides (CpG DNA) rescue WEHI-231 cells from anti-IgM-induced cell cycle arrest and apoptosis. Anti-IgM rapidly elevated the levels of NFkappaB p50/c-Rel heterodimers followed by a decline of p50/c-Rel heterodimers by 3 h and a concomitant increase of p50/p50 homodimers. In contrast, CpG DNA induced and maintained the levels of p50/c-Rel heterodimers in the presence or absence of anti-IgM, while control non-CpG DNA failed to induce NFkappaB activation. Anti-IgM induced IkappaB alpha degradation followed by increased IkappaB alpha protein levels. The levels of IkappaB beta were increased after anti-IgM treatment. In contrast, CpG DNA, but not non-CpG DNA, induced sustained IkappaB alpha and IkappaB beta degradation in the presence or absence of anti-IgM. Inhibition of IkappaB degradation blocked CpG DNA-induced NFkappaB activation and expression of c-myc. Prevention of NFkappaB activation by inhibiting IkappaB degradation also suppressed the ability of CpG DNA to rescue WEHI-231 cells from anti-IgM-induced apoptosis. These results indicate that CpG DNA-mediated sustained activation of NFkappaB depends on the degradation of IkappaB alpha and IkappaB beta and is required for the CpG DNA-mediated anti-apoptosis gene expression and the protection against anti-IgM-induced apoptosis of WEHI-231 cells.

L16 ANSWER 9 OF 17 MEDLINE
AN 1998183875 MEDLINE
TI Identification of peptide ligands for the antigen binding receptor expressed on human B-cell lymphomas.
AU Renschler M F; Dower W J; Levy R
SO METHODS IN MOLECULAR BIOLOGY, (1998) 87 209-34.
Journal code: BU3; 9214969. ISSN: 1064-3745.

L16 ANSWER 10 OF 17 MEDLINE
AN 96128651 MEDLINE
TI Evidence for invariant chain 85-101 (CLIP) binding in the antigen binding site of MHC class II molecules.

AU Bangia N; Watts T H
SO INTERNATIONAL IMMUNOLOGY, (1995 Oct) 7 (10) 1585-91.
Journal code: AY5; 8916182. ISSN: 0953-8178.
AB The region of invariant chain encompassing residues 81-104 is critical for association with MHC class II molecules. This segment of invariant chain, termed CLIP for Class II-associated invariant chain Peptides, has been shown to inhibit antigenic peptide binding and T cell stimulation. Polymorphism affects the ability of CLIP to inhibit antigenic peptide binding, suggesting that CLIP may occupy the MHC II antigen binding site directly. However, CLIP may also mediate inhibition by binding to an alternate site causing an allosteric change to prevent antigenic peptide binding. The relationship between the apparent dissociation constant in the presence of a competitor (Kapp) and the competitor concentration can be examined to determine the nature of competition between two ligands. In competitive binding experiments between CLIP and antigenic peptide we find a linear dependence of Kapp on competitor concentration. These data are consistent with CLIP and antigenic peptide competing for the same site on the MHC class II molecule, thus arguing against an allosteric mechanism of CLIP inhibition. Mildly acidic conditions are thought to promote peptide loading in the endosome compartment by facilitating CLIP dissociation and enhancing antigenic peptide association. We have compared the effect of acidic pH on the equilibrium binding of murine CLIP and antigenic peptide to MHC class II molecules. Like antigenic peptide, CLIP binding can be greatly enhanced at mildly acidic pH, suggesting that a passive competitive mechanism for CLIP removal may not be sufficient to achieve loading of antigenic peptide in the endosome.

L16 ANSWER 11 OF 17 MEDLINE
AN 95293037 MEDLINE
TI Restoration of endogenous antigen processing in Burkitt's lymphoma cells by Epstein-Barr virus latent membrane protein-1: coordinate up-regulation of peptide transporters and HLA-class I antigen expression.
AU Rowe M; Khanna R; Jacob C A; Argaet V; Kelly A; Powis S; Belich M; Croom-Carter D; Lee S; Burrows S R; +
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 May) 25 (5) 1374-84.
Journal code: EN5; 1273201. ISSN: 0014-2980.
AB Group I Burkitt lymphoma (BL) lines retaining the original BL tumor cell phenotype are unable to present endogenously expressed antigens to HLA class I-restricted cytotoxic T cells (CTL) but can be recognized if the relevant HLA class I/peptide epitope complex is reconstituted at the cell surface by exogenous addition of synthetic target peptide. Endogenous antigen-processing function is restored in BL lines that have undergone Epstein-Barr virus (EBV)-induced drift in culture to the group III phenotype typically displayed by EBV-transformed lymphoblastoid cell lines (LCL) of normal B cell origin. We compared group I versus group III cells for their expression of proteasome components, transporter proteins and HLA-class I antigens, all of which are thought to be involved in the endogenous antigen processing pathway. By Western blot analysis, there were not consistent differences in the low molecular mass protein subunits of proteasomes (lmp)-2, lmp-7 and delta, although the mb-1 proteasome subunit was regularly present at higher levels in group I BL lines relative to group III lines or LCL. By contrast there were marked differences in the expression of peptide transporter-associated proteins (Tap), with down-regulation of Tap-1

and Tap-2 in 8/8 and 7/8 group I BL lines, respectively. Surface levels of HLA class I antigens were also consistently lower in group I cells; this was not associated with an intracellular accumulation of free HLA heavy chains, such as is seen in the Tap-deficient T2 processing-mutant line, but instead reflected a reduced rate of HLA class I synthesis in group I cells. Analysis of EBV gene transfectants of the B lymphoma lines BJAB and BL41 showed that the virus-encoded latent membrane protein-1 (LMP1), which is one of several EBV antigens expressed in group III but not in group I cells, was uniquely able to up-regulate expression both of the Tap proteins and HLA class I. Furthermore, this was accompanied by a restoration of antigen-processing function as measured by the ability of these cells to present an endogenously expressed viral antigen to CTL. These effects of LMP1 were similar to those induced in the same cell lines by interferon-gamma treatment. The results implicate both Tap and HLA class I expression as factors limiting the antigen-processing function of BL cells, and suggest that the accessibility of other EBV-associated malignancies to CTL surveillance may be critically dependent upon their LMP1 status.

L16 ANSWER 12 OF 17 MEDLINE
AN 95269279 MEDLINE
TI Biological response modifiers (BRM) as antigens. III. T cell lines specific for BRM kill tumor cells in a BRM-specific manner.
AU Ozaki S; Okazaki T; Nakao K
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1995 Apr) 40 (4) 219-27. Journal code: CN3; 8605732. ISSN: 0340-7004.
AB In order to investigate tumoricidal effector cells in therapy by biological response modifiers (BRM) such as Propionibacterium acnes, bacillus Calmette-Guerin (BCG), Streptococcus pyogenes and a protein-bound polysaccharide (PSK), we established T cell lines specific for each BRM from BALB/c mice immunized with the corresponding BRM. These T cell lines proliferated and produced interleukin-2 (IL-2) and/or IL-4, but only in the presence of the relevant BRM and BALB/c spleen cells as the antigen and antigen-presenting cells respectively. Cross-functional experiments indicated that each BRM acts as a nominal antigen, but not as a non-specific immunostimulator. In addition, the T cell lines killed Ia-positive syngeneic B lymphoma cells, but only in the presence of the relevant BRM. These experiments excluded the possibility of cytotoxic effects by each BRM. The T cell lines and clones also killed Ia-negative bystander target cells, but only in the presence of both a relevant antigen and antigen-presenting cells. The T cell clones specific for S. pyogenes or P. acnes tested were Thy1+, L3T4+ and Lyt2-. These results indicate that some BRM exert tumoricidal activity by inducing T cells that recognize them as an antigen and kill tumor cells in an antigen-specific manner. The T cells killed tumor targets in either a tumor-necrosis-factor(TNF)-dependent or a TNF-independent manner. The mediator of the latter pathway remains to be elucidated.

L16 ANSWER 13 OF 17 MEDLINE
AN 95054739 MEDLINE
TI Production of two monoclonal antibodies (FB1 and FB21) useful for the identification of human B lymphocytes in formalin-fixed, paraffin-embedded tissues.
AU Nozawa Y; Abe M; Ohno H; Fukuhara S; Wakasa H
SO JOURNAL OF PATHOLOGY, (1994 Aug) 173 (4) 347-54.

Journal code: JLB; 0204634. ISSN: 0022-3417.

AB Two monoclonal antibodies (FB1 and FB21) reactive in formalin-fixed, paraffin-embedded tissue sections are reported in this paper. FB1 and FB21 recognize a cytoplasmic antigen and a surface antigen of B cells, respectively. FB1 reacts with mantle zone (MZ) B cells, germinal centre (GC) cells, and marginal zone (MrZ) B cells, but not with T cells in lymphoid tissues. FB21 reacts with MZ B cells, GC cells in lymphoid tissues, and T cells of peripheral blood, but not with MrZ B cells in the spleen. Neither monoclonal antibody (MoAb) reacts with monocytes, granulocytes, or plasma cells. FB1 reacted with all the B-cell lymphomas tested and with CD20-positive Reed-Sternberg cells in two of five cases of Hodgkin's disease, but not with multiple myelomas or T-cell lymphomas. FB21 reacted with B-cell lymphoma in 20 of 22 cases, but not with multiple myelomas, T-cell lymphomas, or Reed-Sternberg cells of Hodgkin's disease. Immunoprecipitation studies revealed that FB1 recognizes the same two polypeptide chains that are recognized by L26 and is a member of the CD20 antibody cluster. FB21 was thought to recognize a sialic acid-dependent carbohydrate epitope and this was confirmed at the Fifth International Conference on Human Leukocyte Differentiation Antigens (Boston, 1993). FB21 did not react with splenic MrZ B cells and was different from the pan B markers reported previously [CD20 (L26), CD45RA (MB1), and CD74 (LN-2)]. FB21 recognizes a subset of B cells and appears to be closely related to CD75/76 antibodies. FB1 and FB21 are useful MoAbs for the diagnosis and analysis of B-cell lymphomas.

L16 ANSWER 14 OF 17 MEDLINE
AN 94045463 MEDLINE
TI Antigen-induced B lymphocyte activation involves the p21ras and ras.GAP signaling pathway.
AU Lazarus A H; Kawauchi K; Rapoport M J; Delovitch T L
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1993 Nov 1) 178 (5) 1765-9.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
AB Ligation of a B lymphocyte surface immunoglobulin (sIg) antigen receptor (AgR) by its specific Ag ligand initiates a signaling pathway that culminates in B cell activation. However, many events of this pathway have not been elucidated. Here we present three novel findings that demonstrate directly that AgR-mediated signaling in B cells functions by the p21ras/ras.GAP-dependent pathway. First, stimulation of TA3 7.9 Ag-specific murine B lymphoma cells for 2 min with either Ag or F(ab')2 anti-IgM induces p21ras activation as measured by an increase in the GTP/GDP ratio of its bound nucleotides. This activation of p21ras does not occur via a change in its guanine nucleotide exchange rate. Second, Ag stimulation results in the inhibition of activity of p120 ras.GAP, a protein that regulates p21ras activation. Tyrosine phosphorylation of ras.GAP occurs within 1 min after Ag stimulation but is no longer detectable at 20 min after stimulation, at which time ras.GAP activity remains inhibited. Thus, tyrosine phosphorylation of ras.GAP is not required for the inhibition of its activity. Third, despite the role proposed for a ras.GAP-associated p190 protein in the control of ras.GAP activity in B cells, p190 was not detectable either in anti-ras.GAP immunoprecipitates of [35S]methionine labeled lysates of Ag-stimulated or -unstimulated 7.9 cells or as a tyrosine phosphoprotein in Western blots of anti-ras.GAP immunoprecipitates of Ag-stimulated 7.9 cell lysates. Inasmuch as the TA3 7.9 B lymphoma is representative of a mature, sIgM-bearing B cell, our

observations raise the intriguing possibility that the capacity of p190 to associate with ras.GAP and regulate the activities of ras.GAP and p21ras in a B cell is dependent on the stage of differentiation of the B cell.

L16 ANSWER 15 OF 17 MEDLINE
AN 93145721 MEDLINE
TI V-rel and C-rel modulate the expression of both bursal and non-bursal antigens on avian B-cell lymphomas.
AU Humphries E H; Zhang G
SO CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY, (1992) 182 475-83.
Journal code: DWQ; 0110513. ISSN: 0070-217X.

L16 ANSWER 16 OF 17 MEDLINE
AN 91131192 MEDLINE
TI Histomorphologic and immunophenotypic spectrum of primary gastro-intestinal B-cell lymphomas.
AU Mielke B; Moller P
SO INTERNATIONAL JOURNAL OF CANCER, (1991 Feb 1) 47 (3) 334-43.
Journal code: GQU; 0042124. ISSN: 0020-7136.
AB In order to compare primary gastro-intestinal (GI) B-cell lymphomas histomorphologically and immunophenotypically with orthologous steps of B-cell differentiation within the mucosa-associated lymphoid tissue (MALT) of the GI tract, a comprehensive panel of well characterized leucocyte differentiation antigens was composed. It comprised immunoglobulin constituents CD5, CD10, CD11c, CD20, CD23, CD24, CD30, CDw32, CD38, CD39, CDw75, CD76, and vimentin. These antigens yield characteristic immunoprofiles for the following B-cell compartments of the MALT, per se closely linked to cytologically distinct B-cell phenotypes: mantle zone (MZ), extrafollicular compartment (EF), follicle center (FC), and plasma-cell compartment (PC). An unselected series of 31 MALT B lymphomas (13 of low and 18 of high grade malignancy) was classified histologically in routine preparations and subsequently characterized immunohistochemically using fresh frozen tissue, monoclonal antibodies (MAbs) against the antigen panel listed above, and an indirect immunoperoxidase method. The final classification considered both morphology and immunoprofile of tumor cells. Ten tumors were "typical" in both respects: 2 closely corresponded to MZ, 5 to EF, 2 to FC and 1 to PC. The remaining 21 cases were characterized as "atypical" because of anaplastic cytology and/or abnormal co-expression and/or loss of antigens. A hybrid EF/FC phenotype was most frequently observed together with centrocyte-like or centrocytic anaplastic cytology of tumor cells. We conclude that MALT B-cell neoplasia comprises a broad spectrum of histo- and immunophenotypes ranging from well differentiated forms closely mimicking normal B-cell development to highly abnormal tumors which cannot be subclassified.

L16 ANSWER 17 OF 17 MEDLINE
AN 91077454 MEDLINE
TI Combined syngeneic bone marrow transplantation and immunotherapy of a murine B-cell lymphoma: active immunization with tumor-derived idiotypic immunoglobulin.
AU Kwak L W; Campbell M J; Zelenetz A D; Levy R
SO BLOOD, (1990 Dec 1) 76 (11) 2411-7.
Journal code: A8G; 7603509. ISSN: 0006-4971.
AB Recurrence of the underlying malignancy remains a major cause of

treatment failure after autologous bone marrow transplantation (BMT) for patients with lymphoma. In this regard, we have developed an immunotherapeutic approach designed to induce resistance against residual tumor cells persisting after BMT. Previous studies in the model system of 38C13, a lethal B-cell lymphoma of C3H origin, have shown that active immunization with purified tumor-derived surface immunoglobulin (Id), as a tumor-associated antigen, produces resistance to tumor growth. Id immunization of lethally irradiated mice at 3 or 5 weeks after reconstitution with syngeneic bone marrow resulted in significantly prolonged survival after tumor challenge compared with nonspecifically immunized controls. Low levels of idiotype-specific antibody were also demonstrated in the sera of specifically immunized mice at this early time, when other functional studies in the literature of immunocompetence after syngeneic reconstitution might have predicted incomplete recovery. Immunization of mice before lethal irradiation and syngeneic marrow reconstitution also induced significant resistance to tumor challenge, suggesting the persistence of established host antitumor immunity through total body irradiation. These studies demonstrate the feasibility of id immunization in conjunction with bone marrow transplantation.

=> fil hom
FILE 'HOME' ENTERED AT 12:26:18 ON 04 FEB 2002

FILE 'CABA, AGRICOLA, CROPU, CROPB' ENTERED AT 09:03:27 ON 05 FEB 2002

L1 6 S PLANT AND B(1W)LYMPHOMA
L2 5 DUP REM L1 (1 DUPLICATE REMOVED)

L2 ANSWER 1 OF 5 CABA COPYRIGHT 2002 CABI DUPLICATE 1
ACCESSION NUMBER: 1999:64766 CABA
DOCUMENT NUMBER: 991604502
TITLE: Rapid production of specific vaccines for lymphoma by expression of the tumor-derived single-chain Fv epitopes in tobacco **plants**
AUTHOR: McCormick, A. A.; Kumagai, M. H.; Hanley, K.; Turpen, T. H.; Hakim, I.; Grill, L. K.; Tuse, D.; Levy, S.; Levy, R.
CORPORATE SOURCE: Biosource Technologies, Inc., 3333 Vacavalley Parkway, Suite 1000, Vacaville, CA 95688, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999) Vol. 96, No. 2, pp. 703-708. 50 ref.
ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rapid production of protein-based tumor-specific vaccines for the treatment of malignancies is possible with the **plant**-based transient expression system described here. A modified tobamoviral vector was created that encodes the idiotype-specific single-chain Fv fragment (scFv) of the immunoglobulin from the 38C13 mouse **B** cell **lymphoma**. Infected Nicotiana benthamiana **plants** contained high levels of secreted scFv protein in the extracellular compartment. This material reacted with an anti-idiotype antibody by Western blotting, ELISA, and affinity chromatography, suggesting that the **plant**-produced 38C13 scFv protein was properly folded in solution. Mice vaccinated with the affinity-purified 38C13 scFv generated > 10 micro g/ml anti-idiotype immunoglobulins. These mice were protected from challenge by a lethal dose of the syngeneic 38C13 tumor, similar to mice immunized with the native 38C13 IgM-keyhole limpet hemocyanin conjugate vaccine. This rapid production system for generating tumor-specific protein vaccines may provide a viable strategy for the treatment of non-Hodgkin's lymphoma.

L2 ANSWER 2 OF 5 CABA COPYRIGHT 2002 CABI
ACCESSION NUMBER: 1999:104127 CABA
DOCUMENT NUMBER: 990307845
TITLE: Induction of apoptosis and inhibition of proliferation in human tumor cells treated with extracts of Uncaria tomentosa
AUTHOR: Sheng YeZhou; Pero, R. W.; Amiri, A.; Bryngelsson, C.; Sheng, Y. Z.
CORPORATE SOURCE: Department of Cell and Molecular Biology, Section for Molecular Ecogenetics, University of Lund, Box 7031, S-220 07 Lund, Sweden.
SOURCE: Anticancer Research, (1998) Vol. 18, No. 5a, pp. 3363-3368. 35 ref.
ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Growth inhibitory activities of novel water extracts of U. tomentosa (C-Med-100) were examined in vitro against 2 human leukaemic cell lines (K562 and HL60) and a human EBV-transformed **B lymphoma** cell line (Raji). The proliferative capacities of HL60 and Raji cells were strongly suppressed in the presence of C-Med-100; K562 was more resistant. The antiproliferative effect was confirmed using the clonogenic assay, which showed a very close correlation between C-Med-100 concentration and the surviving fraction. The suppressive effect of the extract on tumour cell growth appeared to be mediated through induction of apoptosis which was demonstrated by characteristic morphological changes, internucleosomal DNA fragmentation after agarose gel electrophoresis and DNA fragmentation quantification. C-Med-100 induced a delayed type of apoptosis becoming most dose-dependently prominent after 48 h of exposure. Both DNA single and double strand breaks were increased 24 h after C-Med-100 treatment, which suggested a well-established linkage between the DNA damage and apoptosis. The induction of DNA strand breaks coupled to apoptosis may explain the extract-mediated inhibition of growth.

L2 ANSWER 3 OF 5 CABA COPYRIGHT 2002 CABI
ACCESSION NUMBER: 1998:49372 CABA
DOCUMENT NUMBER: 980703611
TITLE: Water permeability of plasma membranes of cultured rice, grape, and CH27 cells measured dielectrically
AUTHOR: Ishikawa, E.; Miyawaki, O.; Nakamura, K.
CORPORATE SOURCE: Department of Applied Biological Chemistry, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan.
SOURCE: Bioscience, Biotechnology and Biochemistry, (1997) Vol. 61, No. 11, pp. 1826-1830. 30 ref. ISSN: 0916-8451
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The capacitance of suspension cultured rice and grape cells (Vitis sp.), and CH27 cells originated from murine **B**-cell **lymphoma** was measured in the frequency range of 0.2 to 10 MHz. The relationship between the increase in capacitance caused by the presence of cells at 0.4 MHz, DELTA C, and cell density was linear. Measurement of capacitance was useful in the assessment of transitional changes in cell volume under external osmotic stress with the addition of sucrose. From the course of volume changes with such stress, the water permeabilities of the plasma membrane (Lp) were 0.015, 0.020 and 0.090 pm/(s.Pa) at 25 deg C for rice, grape and CH27 cells, respectively. It is suggested that the smaller Lp recorded for **plant** cells may explain the difficulty in preservation of **plant** cells by freezing. From the temperature dependence of Lp, the apparent activation energies were calculated to be 12.0 plus or minus 2.9 and 13.0 plus or minus 5.2 kcal/mol for rice cells and CH27 cells, respectively.

L2 ANSWER 4 OF 5 CROPU COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1991-83243 CROPU H S
TITLE: Effects of 2,4,5-Trichlorophenoxyacetic Acid, Pentachlorophenol, Methylprednisolone, and Freund's Adjuvant on 2-Hydroxyethylnitrosourea Carcinogenesis in MRC-Wistar Rats.

AUTHOR: Mirvish S S; Nickols J; Weisenburger D D; Johnson D; Joshi S S; Kaplan P
LOCATION: Omaha; Lincoln, Neb., USA
SOURCE: J.Toxicol.Environ.Health (32, No. 1, 59-74, 1991) 1 Fig. 3 Tab. 39 Ref.
CODEN: JTEHD6
AVAIL. OF DOC.: Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE 68198-6805, U.S.A. (8 authors).
DOCUMENT TYPE: Journal
LANGUAGE: English
FIELD AVAIL.: LA; CT
AN 1991-83243 CROPU H S
AB MRC-Wistar rats of both sexes were fed on diets containing 98% 2,4,5-T (600 mg/kg diet) or 86% pentachlorophenol (PCP) (500 mg/kg diet) or received methylprednisolone (20 mg/kg i.p. wkly), Freund's adjuvant (0.5 ml i.m. every 3-6 wk) or n- butylnitrosourea (BNU) (300 mg/l in drinking water) alone for 40 wk or together with 2-hydroxyethylnitrosourea (HENU) in drinking water at 75 mg /l. PCP and 2,4,5-T were analyzed for 2,3,7,8-tetrachlorodibenzodioxin and -tetrachlorodibenzofuran, of which large and small amounts were found, respectively. **B**- cell **lymphomas** were found in rats given HENU. PCP, alone or with HENU induced 40-67% of liver cell adenomas in female rats, acting synergistically with HENU.

L2 ANSWER 5 OF 5 CABA COPYRIGHT 2002 CABI
ACCESSION NUMBER: 87:27461 CABA
DOCUMENT NUMBER: 872293093
TITLE: Selective integration of avian leukosis virus in different hematopoietic tissues
AUTHOR: Baba, T. W.; Humphries, E. H.
CORPORATE SOURCE: Dep. Microbiol., Southwestern Med. Sch., Univ. Hlth Sci. Center, 5323 Harry Hines Boulevard, Dallas TX 75235, USA.
SOURCE: Virology, (1986) Vol. 155, No. 2, pp. 557-566. 44 ref.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Haematopoietic tissues from avian leukosis virus (ALV)-infected Hyline SC chickens were examined for integrated viral DNA sequences. Cells were prepared from bone marrow, bursa, spleen, thymus, and peripheral blood. Following the removal of erythrocytes, cellular DNAs from each of these tissues were examined by Southern analysis. During the first few weeks of infection, DNA from the bone marrow contained as many as 0.5 copies of viral DNA per haploid genome. Cells from the bursa and peripheral blood contained between 0.05 and 0.15 copies per haploid genome. In contrast, neither splenic nor thymic DNA contained significant levels of viral DNA sequences even though infected birds developed titres of circulating virus between 105 and 106 IU/ml of plasma. DNA prepared from erythrocytes isolated from the peripheral blood of these birds contained approximately 0.4 copies of integrated viral sequences per haploid genome at 2 weeks after infection. Despite greater levels of integrated sequences in other tissues, by 9 weeks after infection viral sequences were detected only in DNA from bursal lymphocytes. Cells prepared from the spleen and thymus of infected birds were also examined for size distribution, internal complexity and surface expression of

immunoglobulin. None of the populations examined differed from normal, uninfected control preparations. These results suggest that ALV infection occurs primarily in the bone marrow and that the different tissues of the haematopoietic system are selectively infected. These results indicate that ALV infection persists longer in bursal lymphocytes than in other haematopoietic tissues. Previous studies have shown that the lymphoid tumours that develop in White Leghorn chickens following ALV infection are bursal-dependent **B**-cell **lymphomas** that express immunoglobulin M.
The observations presented here offer, in part, an explanation for the restricted phenotype of the lymphoid tumour that develops in the SC chicken, and may also explain the bursal-dependent nature of the ALV-induced lymphoma.

FILE 'HOME' ENTERED AT 09:04:14 ON 05 FEB 2002